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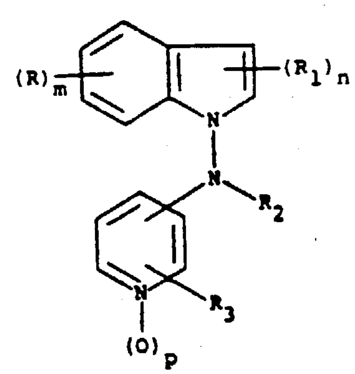
(54) N-(Pyridinyl)-1H-indol-1-amines, a process for their preparation and their use as medicaments.

(57) There are disclosed compounds of the formula



where m is 1 or 2; n is 1 or 2; P is 0 or 1; each R is independently hydrogen, halogen, loweralkyl, loweralkoxy, hydroxy, nitro, amino, loweralkylamino, loweralkylcarbonylamino, cyano, formyl, loweralkoxycarbonyl, loweralkylthio or loweralkoxycarbonylloweralkylthio; each R_1 is independently hydrogen, loweralkyl, loweralkenyl, formyl, loweralkylcarbonyl, arylloweralkylcarbonyl, arylcarbonyl, halogen, arylloweralkenyl, arylloweralkyl, heteroarylloweralkenyl, heteroarylloweralkyl, cyanoloweralkenyl, cyanoloweralkyl, methox-

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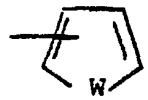
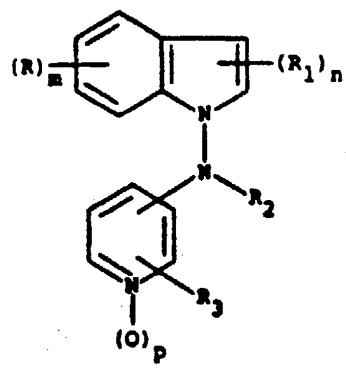
yloweralkenyl, methoxyloweralkyl, loweralkoxycarbonylloweralkenyl, loweralkoxycarbonylloweralkyl, cycloalkylloweralkenyl or cycloalkylloweralkyl, the term heteroaryl signifying a group of the formula



where W is O, S, NH or. CH=N, cyano, -CH(OH)R_4, -C(OH)R_4R_5 or -CH_2OR_5, R_4 being hydrogen, loweralkyl, arylloweralkyl or aryl and R_5 being loweralkyl, arylloweralkyl or aryl; each R_2 is independently hydrogen, loweralkyl, loweralkenyl, loweralkynyl, loweralkoxycarbonylloweralkyl, loweralkylaminocarbonylloweralkyl, aminocarbonylloweralkyl, arylloweralkyl, phenyl, nitrophenyl, cyanophenyl, trifluoromethylphenyl, aminophenyl, loweralkanoylaminophenyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, loweralkylaminocarbonyl, arylloweralkylaminocarbonyl, arylaminocarbonyl, alkanoyl, arylloweralkanoyl, aroyl, alkenoyl, alkynoyl or -R_6-NR$'$R$''$ where R_6 is loweralkylene, loweralkenylene or loweralkynylene and R$'$ and R$''$ are each independently loweralkyl or alternatively the group -NR$'$R$''$ as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl; and R_3 is hydrogen, nitro, amino, halogen, loweralkanoylamino, arylloweralkanoylamino, aroylamino, alkylamino, arylloweralkylamino or loweralkyl and a process for their preparation. The compounds are useful for enhancing memory and also as analgesic and antidepressant agents.

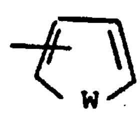
N-(Pyridinyl)-1H-indol-1-amines, a process for their preparation and their use as medicaments.

The present invention relates to novel compounds of the formula



I

where m is 1 or 2; n is 1 or 2; P is 0 or 1; each R is independently hydrogen, halogen, loweralkyl, loweralkoxy, hydroxy, nitro, amino, loweralkylamino, loweralkylcarbonylamino, cyano, formyl, loweralkoxycarbonyl, loweralkylthio or loweralkoxycarbonylloweralkylthio; each R_1 is independently hydrogen, loweralkyl, loweralkenyl, formyl, loweralkylcarbonyl, arylloweralkylcarbonyl, arylcarbonyl, halogen, arylloweralkenyl, arylloweralkyl, heteroarylloweralkenyl, heteroarylloweralkyl, cyanoloweralkenyl, cyanoloweralkyl, methoxyloweralkenyl, methoxyloweralkyl, loweralkoxycarbonylloweralkenyl, loweralkoxycarbonylloweralkyl, cycloalkylloweralkenyl or cycloalkylloweralkyl, the term heteroaryl signifying a group of the formula



where W is O, S, NH or CH=N, cyano, -CH(OH)R_4, -C(OH)R_4R_5 or -CH_2OR_5, R_4 being hydrogen, loweralkyl, arylloweralkyl or aryl and R_5 being loweralkyl, arylloweralkyl or aryl; each R_2 is independently hydrogen, loweralkyl, loweralkenyl, loweralkynyl, loweralkoxycarbonylloweralkyl, loweralkylaminocarbonylloweralkyl, aminocarbonylloweralkyl, arylloweralkyl, phenyl, nitrophenyl, cyanophenyl, trifluoromethylphenyl, aminophenyl, loweralkanoylaminophenyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, loweralkylaminocarbonyl, arylloweralkylaminocarbonyl, arylaminocarbonyl, alkanoyl, arylloweralkanoyl, aroyl, alkenoyl, alkynoyl or -R_6-NR$'$R$''$ where R_6 is loweralkylene, loweralkenylene or loweralkynylene and R$'$ and R$''$ are each independently loweralkyl or alternatively the group -NR$'$R$''$ as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl; and R_3 is hydrogen, nitro, amino, halogen, loweralkanoylamino, arylloweralkanoylamino, aroylamino, alkylamino, arylloweralkylamino or loweralkyl; which compounds are useful for enhancing memory and also as analgesic and antidepresant agents; and pharmaceutical compositions comprising an effective amount of such a compound.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo, optical, and geometrical isomers thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof such as for instance hydrates.

The following general rules of terminology shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term loweralkyl denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said loweralkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight-and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term loweralkoxy denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said loweralkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight-and branched-chain pentoxy and hexoxy.

Unless otherwise stated or indicated, the term halogen shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term aryl shall means a phenyl group having 0, 1, 2 or 3 substituents each of which being independently loweralkyl, loweralkoxy, halogen, CF_3, NO_2 or CN.

Unless otherwise stated or indicated, the term alkyl shall mean a saturated hydrocarbon group of 1 to 20 carbon atoms, the term alkenyl shall mean a hydrocarbon group of 1-20 carbon atoms having one or more carbon-carbon double bonds, and the term alkynyl shall mean a hydrocarbon group of 1-20 carbon atoms having one or more carbon-carbon triple bonds.

The term loweralkanoic acid shall mean a carboxylic acid in which the carboxyl group is attached to hydrogen or an alkyl group of from 1 to 5 carbon atoms.

The term loweralkanoyl shall mean a group obtained by removing a hydroxy group from the carboxyl group of a loweralkanoic acid, and thus it includes for instance formyl, acetyl and the like.

The term arylloweralkanoyl shall mean a loweralkanoyl group having an aryl substituent thereon, the term loweralkanoyl and aryl having the respective meanings defined above.

The term aroyl shall mean arylcarbonyl, an example being benzoyl.

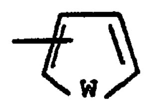
The term arylloweralkyl shall mean a loweralkyl group having an aryl substituted thereon, the terms loweralkyl and aryl having the respective meanings defined above.

The terms alkanoyl, alkenoyl and alkynoyl shall mean groups obtained by removing a hydroxy group from the carboxyl group of alkanoic acid, alkenoic acid and alkynoic acid, respectively. Thus, for instance, linoleyl group derived from linoleic acid is an example of the term alkenoyl as defined above.

The term acyl shall mean loweralkanoyl or arylloweralkanoyl as defined above.

The term cycloalkyl in each occurrence shall mean an alicyclic group of 3 to 7 ring carbons.

The term heteroaryl in each occurrence shall mean a group of the formula

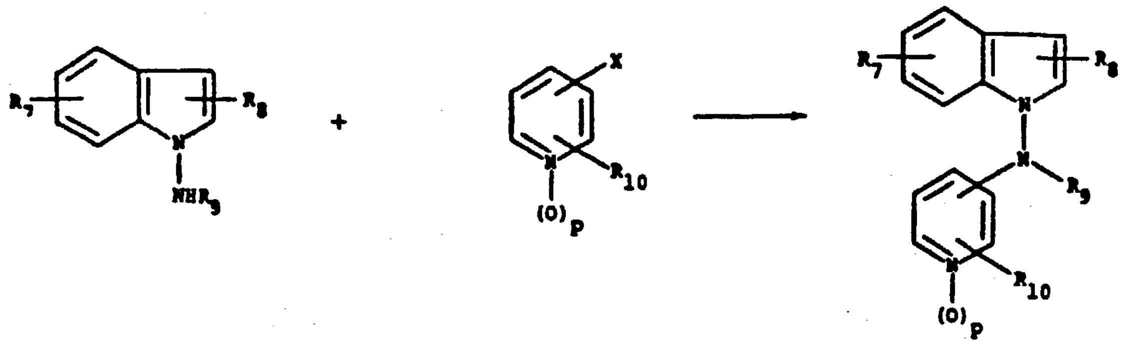


where W is O, S, NH or CH=N.

The compounds of formula (I) of this invention can be synthesized by following or combining one or more of the steps described below, not necessarily in the order presented. For the sake of simplification, the description of synthetic schemes is presented below for compounds in which m=n=1, but it will be apparent that other compounds in which m and/or n is 2 can be prepared by utilizing the synthetic schemes and making necessary modifications. Throughout the description of the synthetic steps, the definitions of R, R_1 through R_6, R', R'', m, n and p are as given above unless otherwise stated or indicated, and other nomenclatures appearing below shall have the same meanings defined in their respective first appearances unless otherwise stated or indicated.

STEP A

A compound of formula (II) where R_7 is H, halogen, loweralkyl, loweralkoxy, nitro, cyano, formyl, loweralkylthio or loweralkoxycarbonylloweralkylthio and R_8 is H, loweralkyl, halogen or cyano and R_9 is H or loweralkyl is reacted with a compound of formula (III) where X is chlorine or fluorine and R_{10} is H, NO_2, halogen or loweralkyl to afford a compound of formula (IV).

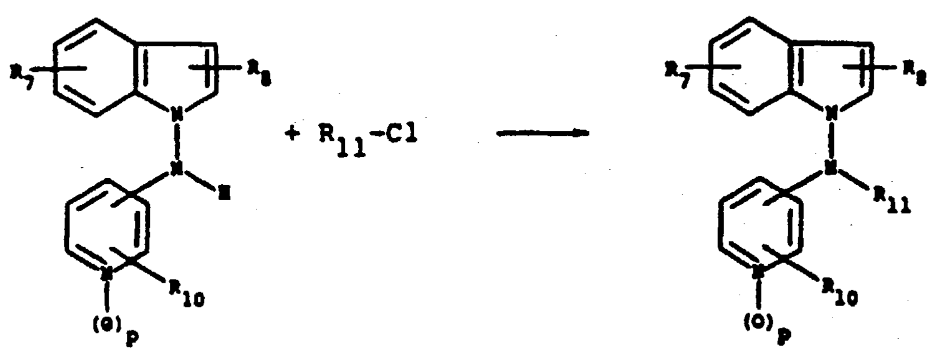


(II) (III) (IV)

Said reaction is typically conducted in an ethereal solvent such as bis(2-methoxyethyl)ether, diethyl ether, dimethoxy ether, dioxane or tetrahydrofuran or polar aprotic solvent such as dimethylformamide, dimethylacetamide, hexamethylphosphoramide or dimethylsulfoxide or protic solvent such as ethanol or isopropanol at a temperature of between about 20°C and 150°C.

STEP B

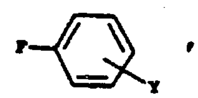
A compound of formula IVa obtained from STEP A is treated with a strong base such as sodium hydride or potassium hydride in a suitable solvent such as polar aprotic solvent including dimethylformamide, dimethylsulfoxide and ethereal solvents or aromatic hydrocarbon at a temperature of between about -10° and 50°, preferably 0-25° to form the anion of IVa, which is reacted with a chloride compound of the formula R_{11}-Cl, where R_{11} is loweralkyl, loweralkoxycarbonylloweralkyl, loweralkenyl, loweralkynyl, arylloweralkyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl or aryloxycarbonyl at a temperature of between about -10° and 80°, preferably between 0° and 25° to obtain a compound of formula V.



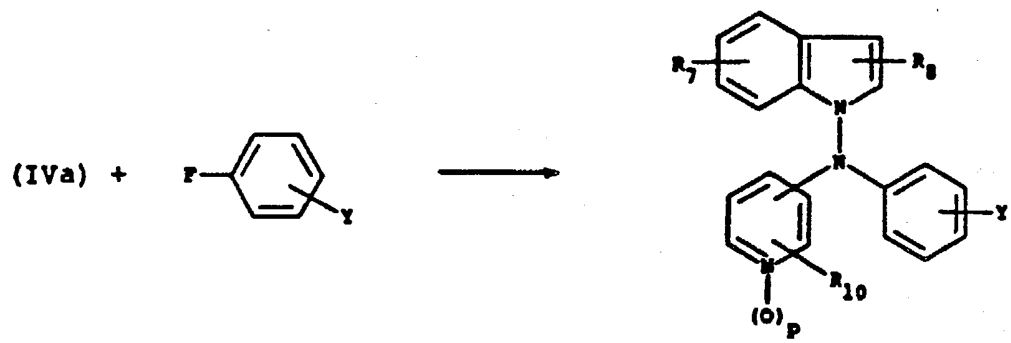
(IVa) (V)

STEP C

The anion of compound IVa prepared as in STEP B is reacted with fluoro-nitrobenzene, cyano-fluorobenzene or fluoro-trifluoromethylbenzene of the formula



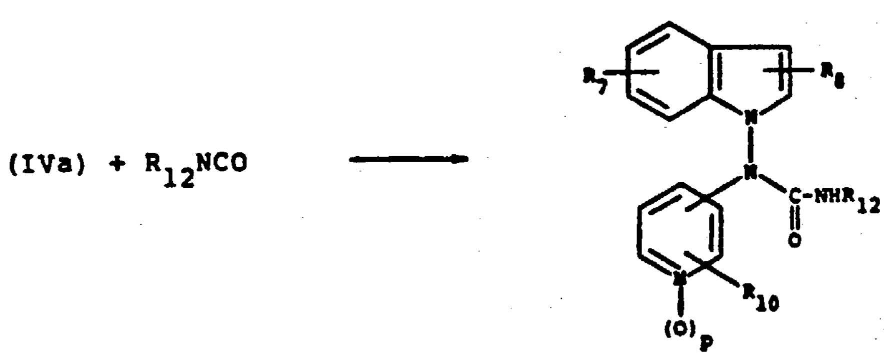
where Y is nitro, cyano or trifluoromethyl to afford a compound of formula VI below. Said reaction is conducted in substantially the same manner as in STEP B.



(VI)

STEP D

Compound IVa is reacted with a loweralkyl isocyanate, arylloweralkyl isocyanate or aryl isocyanate of the formula $R_{12}NCO$ where R_{12} is loweralkyl, arylloweralkyl or aryl to afford a compound of formula VII.

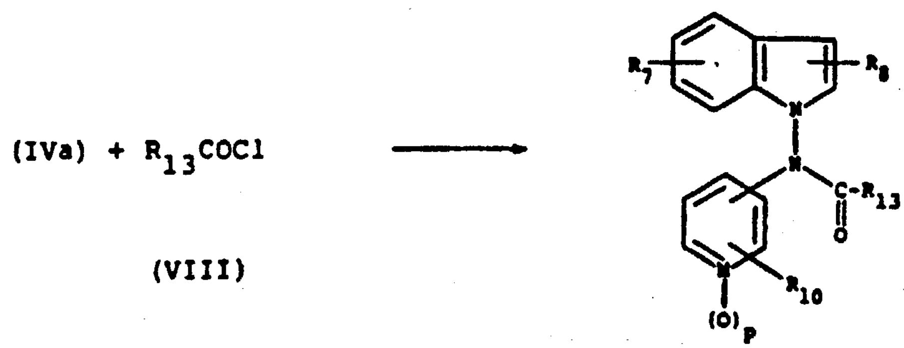


(VII)

Said reaction is typically conducted in a suitable solvent such as aromatic hydrocarbon including benzene, toluene and the like, halogenated hydrocarbon or ethereal solvent at a temperature of about 0-80°, preferably 30-60°C.

STEP E

Compound IVa is reacted with an alkanoyl chloride, arylloweralkanoyl chloride, aroyl chloride, alkenoyl chloride or alkynoyl chloride or formula (VIII) where R_{13} is alkyl, arylloweralkyl, aryl, alkenyl or alkynyl to afford a compound of formula (IX). Said reaction is typically conducted in substantially the same manner as in STEP D.

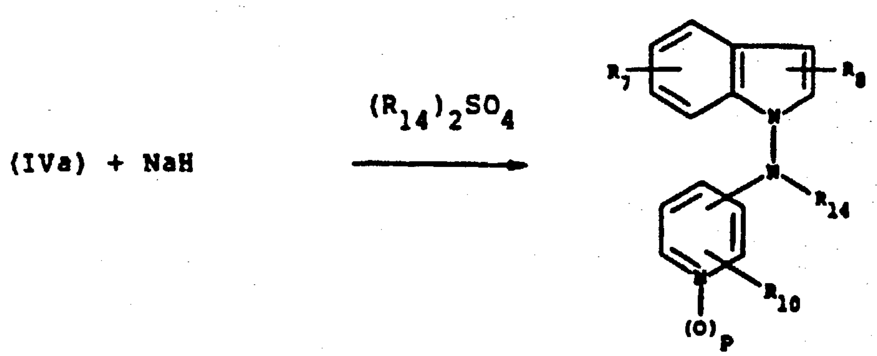


(IX)

Where the compound $R_{13}COCl$ is not commercially available, it is prepared from the corresponding carboxylic acid $R_{13}COOH$ and thionyl chloride in a suitable solvent, for instance, in benzene at the reflux temperature.

STEP F

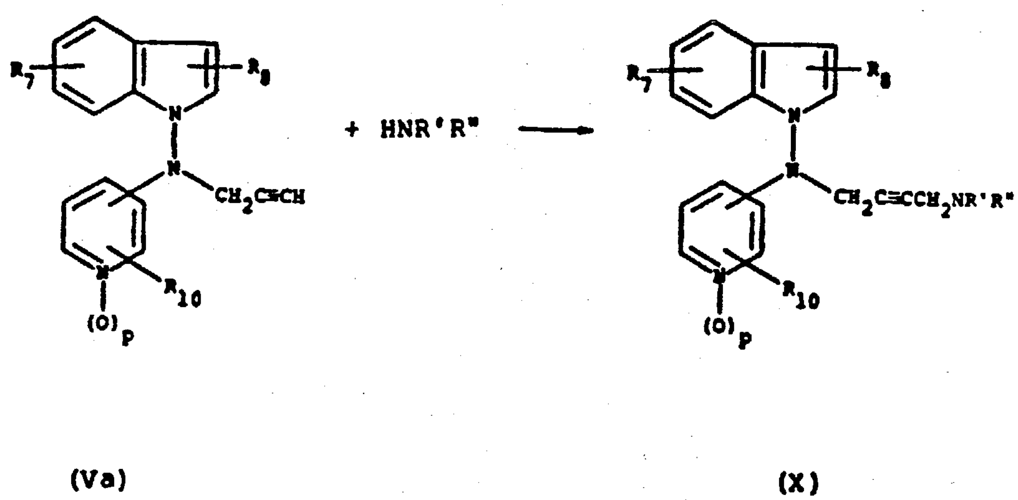
As an alternative to STEP A or B, a compound of formula (IVb) where R_{14} is loweralkyl can be prepared by reacting compound IVa with a strong base such as sodium hydride or potassium hydride and then reacting the product with a diloweralkyl sulfate of the formula $(R_{14})_2SO_4$. Said two steps are conducted under substantially the same conditions as used in STEP B.



(IVb)

STEP G

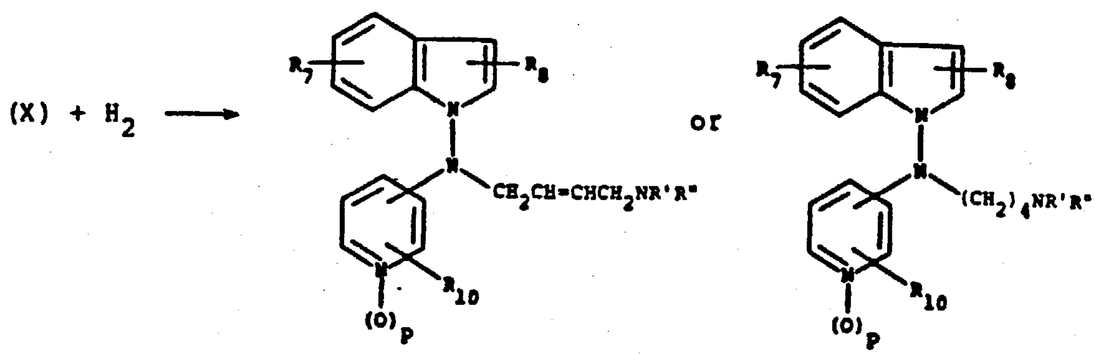
A compound of formula Va obtained in STEP B is subjected to Mannich reaction with formaldehyde and a secondary amine of the formula $HNR'R''$, where R' and R'' are independently loweralkyl or $-NR'R''$ taken together is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl to afford a compound of formula X.



The above reaction can be conducted under conditions usually used in the art for carrying out Mannich reactions. Typically, it is conducted by preparing a mixture of compound Va, paraformaldehyde, $HNR'R''$, cuprous chloride (used as a catalyst) and a suitable medium including ethereal solvents such as dioxane, and heating the mixture at 25-100°.

STEP H

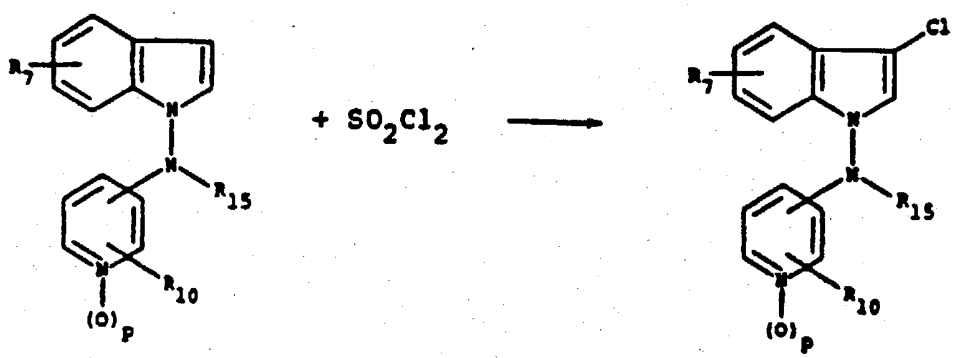
Compound X is catalytically hydrogenated to afford a compound of formula XI or XII by making a suitable selection of reaction conditions in a manner known to the art.



(XI) (XII)

STEP I

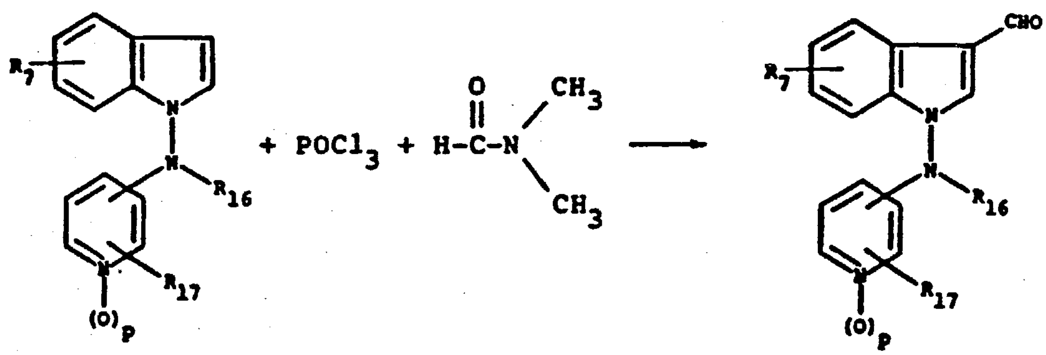
As an alternative to the foregoing steps, a compound of formula XIV where R_{15} is loweralkyl, loweralkoxycarbonylloweralkyl, arylloweralkyl, aryl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, alkanoyl, arylloweralkanoyl or aroyl can be prepared by reacting a compound of formula XIII with a suitable chlorinating agent such as sulfuryl chloride (SO_2Cl_2) in a manner known in the art.



(XIII) (XIV)

STEP J

A compound of formula (XV) where R_{16} is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl, and R_{17} is H, NO_2, halogen or loweralkyl which is prepared by use of one or more of the reaction steps described in this specification is reacted with phosphorous oxychoride and dimethylformamide to afford a compound of formula (XVI).



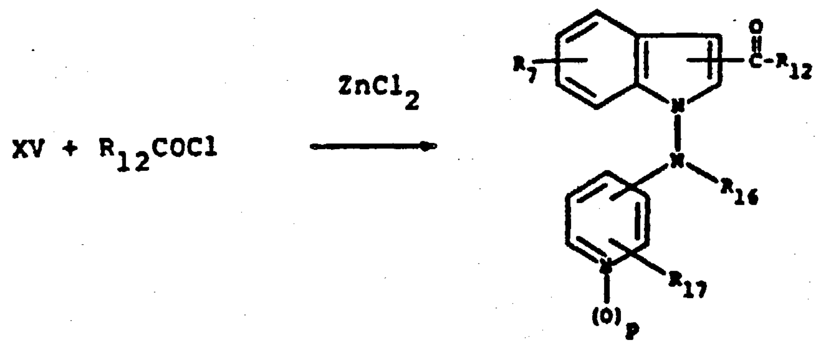
(XV) (XVI)

Said reaction can be conducted under conditions usually used for carrying out Vilsmeier reactions. Typically, it is conducted in a suitable solvent such as halogenated hydrocarbon at a temperature of about 20-100°.

Where the positional isomer of compound XVI in which the formyl group is at the 2-position of the indole ring is desired, compound XV is reacted with secondary butyllithium and the resultant lithio compound reacted with N-formyl-N-methyl-aniline in a manner known in the art.

STEP K

Compound XV is reacted with a loweralkanoyl chloride, arylloweralkanoyl chloride or aroyl chloride of formula $R_{12}COCl$ in the presence of zinc chloride to afford a compound of formula (XVII). Said reaction is typically conducted in a suitable solvent such as halogenated hydrocarbon at a temperature of about 20-100°C.

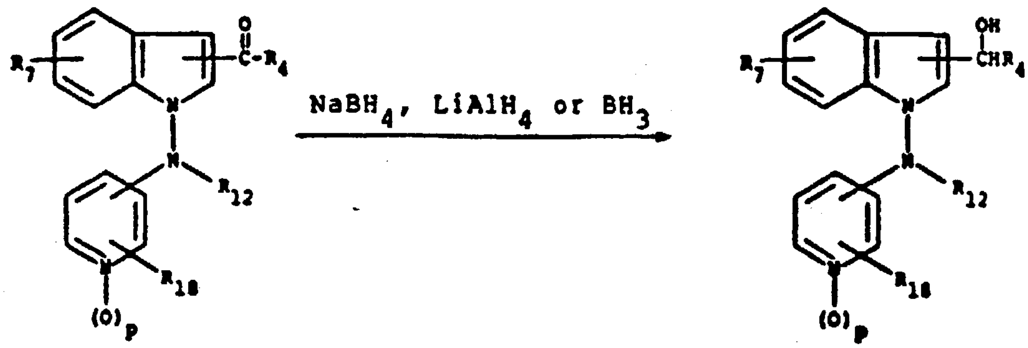


(XVII)

Where the positional isomer of compound XVII in which the group -C(O)R_{12} is at the 2-position of the indole ring is desired, compound XV is reacted with secondary butyllithium and the resultant lithio compound reacted with $R_{12}COCl$ in a manner known to the art.

STEP L

A compound of formula XVIII below where R_{18} is H, halogen or loweralkyl is reduced to a compound of formula XIX below with $NaBH_4$, $LiAlH_4$ or borane complexes.

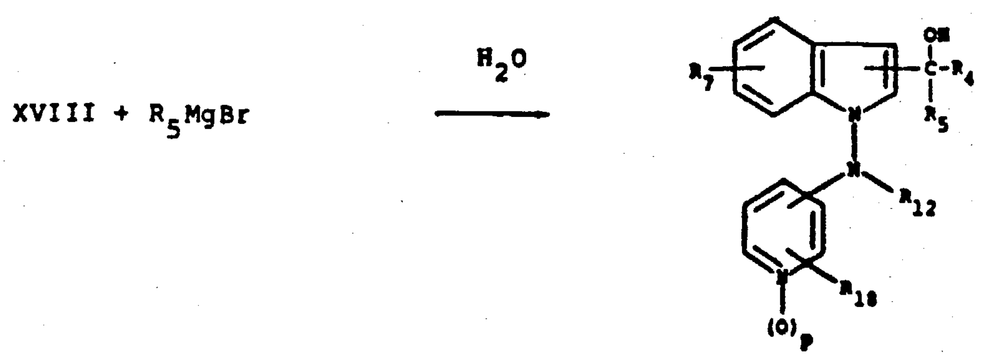


(XVIII) (XIX)

When $NaBH_4$ is used, said reduction is conducted typically in a lower aliphatic alcohol such as isopropanol or ethanol or loweralkanoic acid at a temperature of about 0-80°. After the reaction, water is added to the reaction mixture. When $LiAlH_4$ is used, said reduction is conducted typically in an ethereal solvent such as tetrahydrofuran or ether at a temperature of about 0-80°. When borane complexes are used, the reaction temperature is typically 0-80°C.

STEP M

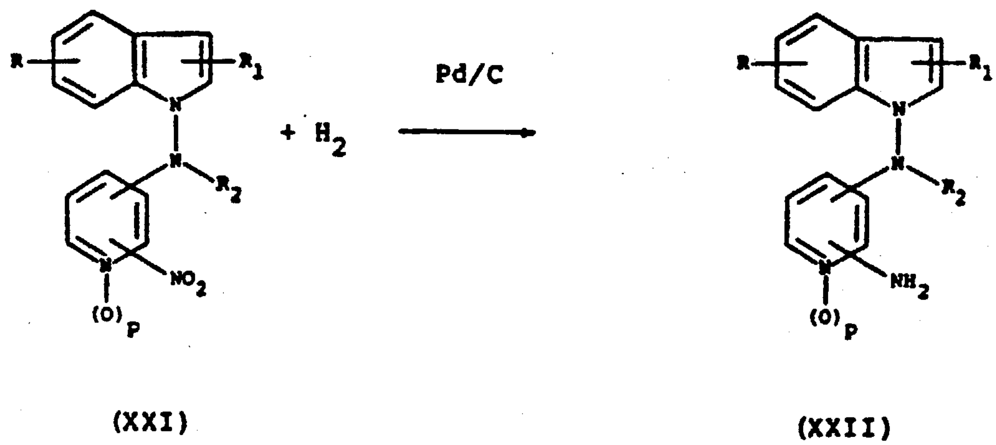
Compound XVIII is reacted with a Grignard reagent of the formula R_5MgBr and the product is thereafter hydrolyzed to afford a compound of formula XX below.



(XX)

STEP N

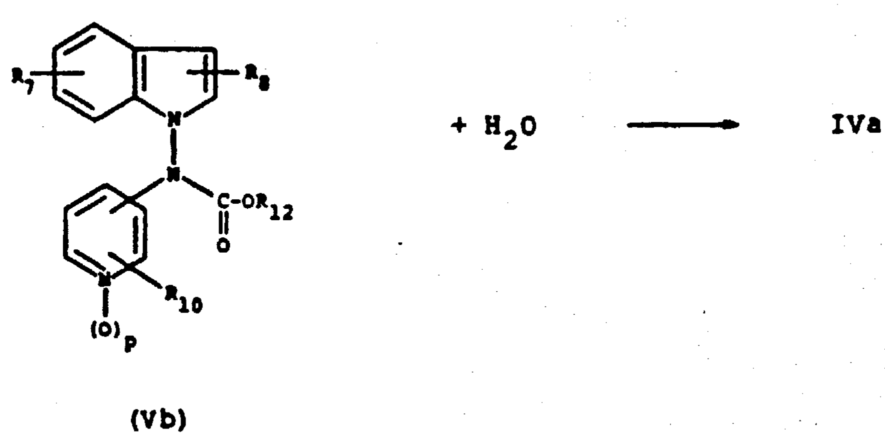
A compound of formula XXI which is prepared by use of one or more of the reaction steps described in this specification is catalytically hydrogenated with hydrogen gas and a suitable catalyst such as palladium on carbon to afford a compound of formula (XXII).



Said catalytic hydrogenation is typically conducted in a suitable solvent such as loweralkanol or loweralkyl ester of loweralkanoic acid at a temperature of 20-50°C.

STEP O

As an alternative to the foregoing steps, compound IVa can be prepared by hydrolyzing a carbamate compound of formula Vb. (Needless to say, the purpose of this STEP is not to reverse aforementioned STEP B in order to regain the starting compound of STEP B. This STEP can be useful, for instance, for the purpose of converting R_8 in formula IVa from hydrogen to 3-chloro. Thus, for this purpose, one can first convert the amino hydrogen in formula IVa to ethoxycarbonyl by use of STEP B or similar to STEP E and then introduce a chlorine atom into the 3-position of the indole ring by use of STEP I and thereafter hydrolyze the resultant product by use of this STEP, instead of conducting the chlorination reaction directly with compound IVa. Similarly, this STEP can also be useful for introducing the group $-COR_{12}$ into the indole ring according to STEP K above or the group -CHO according to STEP J when R_2 is hydrogen.

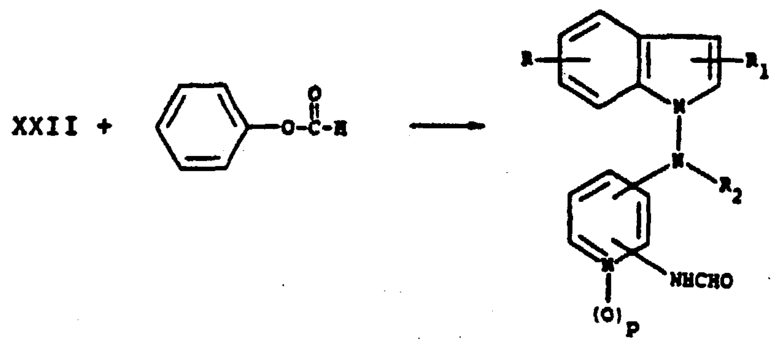


Said hydrolysis is conducted typically by stirring a mixture comprising compound Vb, an alkali such as

NaOH and a suitable medium such as ethanol plus water at a temperature of about 70-100°C.

STEP P

Compound XXII is reacted with phenyl formate to afford a compound of formula (XXIII)

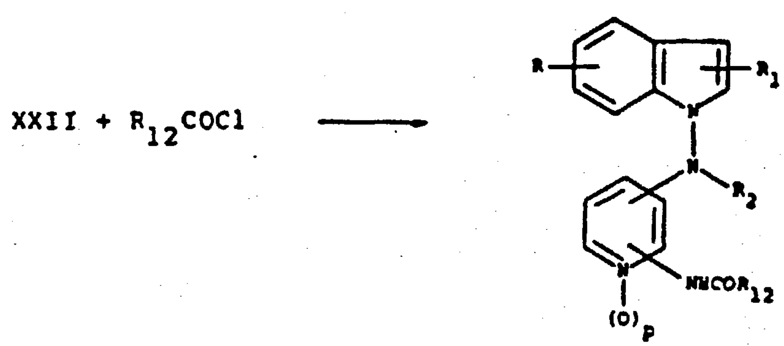


(XXIII)

Typically said reaction is conducted by stirring a solution of compound XXII in excess phenyl formate at a temperature of about 20-50°C. The same reaction can also be conducted with loweralkyl formate under substantially the same conditions.

STEP Q

Compound XXII is reacted with an acyl chloride of the formula $R_{12}COCl$ or acid anhydride of the formula $R_{12}CO-O-COR_{12}$ to afford a compound of formula XXIV.

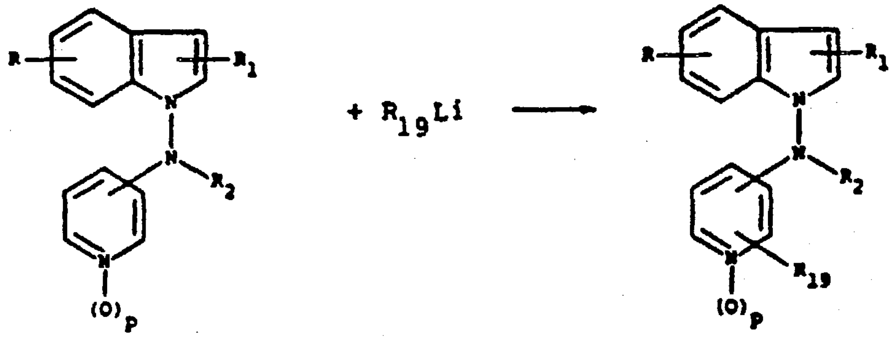


(XXIV)

Said reaction is conducted under substantially the same conditions as used in STEP E.

STEP R

As an alternative to the foregoing steps, a compound of formula XXV where R_1 is H or loweralkyl, and R_2 is loweralkyl, arylloweralkyl, phenyl, nitrophenyl, or trifluoromethylphenyl, can be prepared by reacting a compound of formula (IVc) with a loweralkyl lithium of the formula $R_{19}Li$ where R_{19} is loweralkyl.

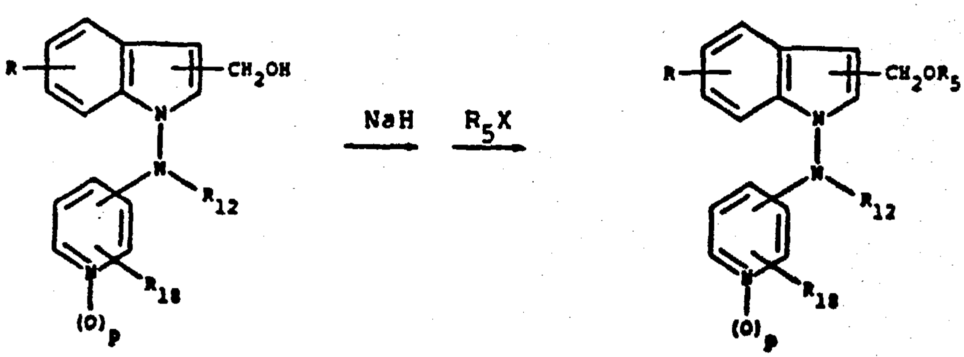


(IVc) (XXV)

Said reaction is usually conducted in a suitable solvent such as ethereal solvent, preferably tetrahydrofuran at a temperature of between about -10° and 50°C.

STEP S

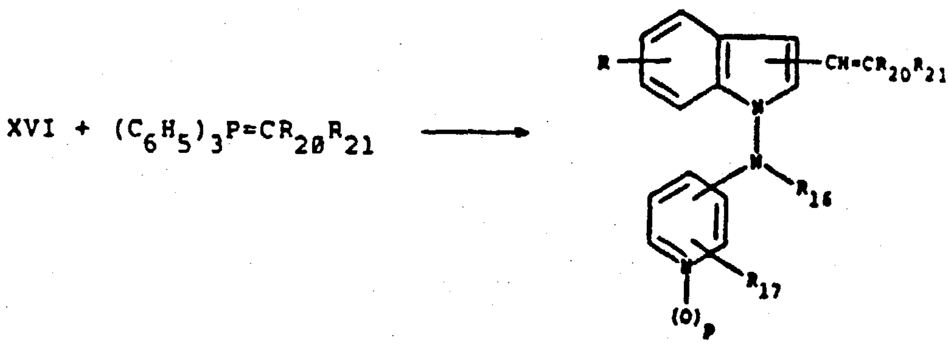
A compound of formula XIXa below is reacted with a strong base such as sodium hydride or potassium hydride and the resultant alkoxide anion is reacted with a halide of the formula R_5X to afford an ether of formula XXVI below. Said two-step procedure is conducted in substantially the same manner as in STEP B above.



(XIXa) (XXVI)

STEP T

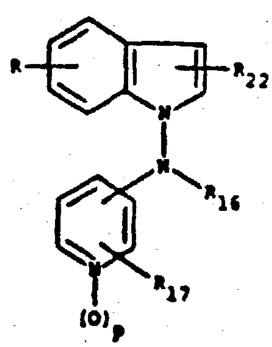
Compound XVI is subjected to Wittig reaction with an ylide of the formula $(C_6H_5)_3P=CR_{20}R_{21}$ to afford a compound of formula XXVII where R_{20} and R_{21} are each independently hydrogen, loweralkyl, aryl, arylloweralkyl, heteroaryl, heteroarylloweralkyl, cyano, methoxy, loweralkoxycarbonyl or together form a cycloalkylidene.



(XXVII)

The above reaction can be conducted under conditions usually used for carrying out Wittig reactions. Thus, the ylide is prepared in a routine manner by first preparing a phosphonium salt from a bromide of the formula $BrCHR_{20}R_{21}$ and triphenylphosphine and thereafter reacting the phosphonium salt with a suitable base such as sodium hydride, potassium tert-butoxide or n-butyllithium in a suitable solvent such as anhydrous ethereal solvent. Thereafter a solution of compound XVI in a suitable solvent such as anhydrous ether is added to the freshly prepared ylide solution and the mixture is stirred at a temperature of between about -10°C and 80°C.

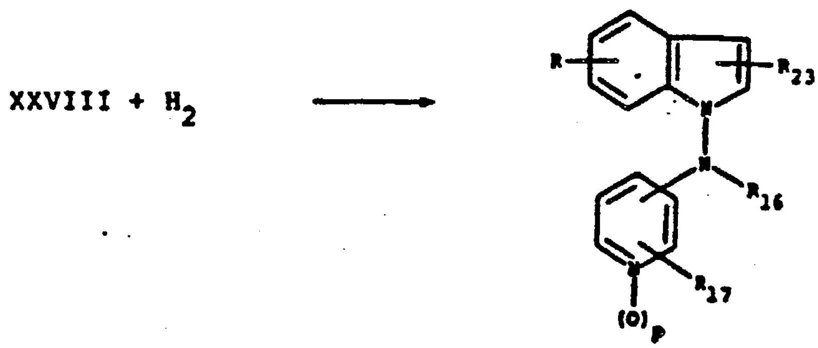
It will be apparent that by making a suitable selection of the groups R_{20} and R_{21} and/or conducting Wittig reaction more than once if necessary, one can obtain compounds of formula XXVIII where the group R_{22} is loweralkenyl, arylloweralkenyl, heteroarylloweralkenyl, cyanoloweralkenyl, methoxyloweralkenyl, loweralkoxycarbonylloweralkenyl, or cycloalkylloweralkenyl.



(XXVIII)

STEP U

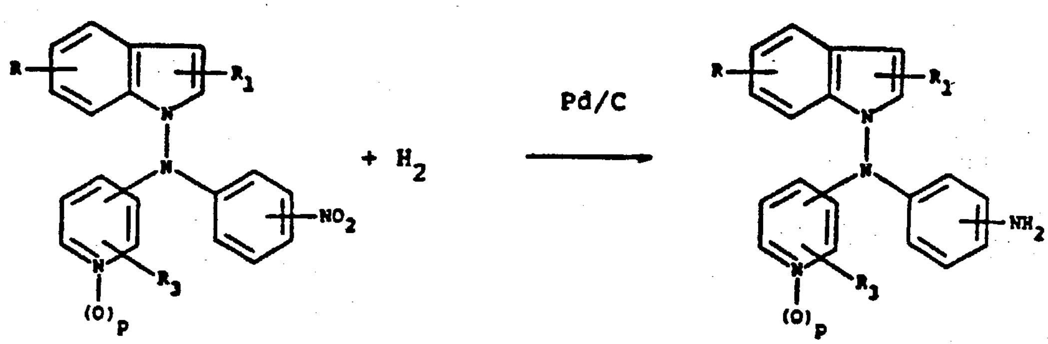
Compound XXVIII is catalytically hydrogenated in a suitable manner known to the art to afford a compound of formula XXIX where R_{23} is loweralkyl, arylloweralkyl, heteroarylloweralkyl, cyanoloweralkyl, methoxyloweralkyl, loweralkoxycarbonylloweralkyl or cycloalkylloweralkyl.



(XXIX)

STEP V

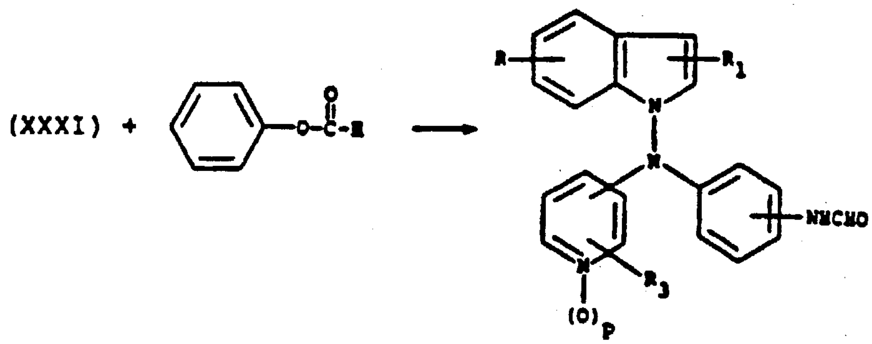
Substantially the same hydrogenation technique as described in STEP N or U can be used to hydrogenate a compound of formula XXX below to afford a compound of formula XXXI below.



(XXX) (XXXI)

STEP W

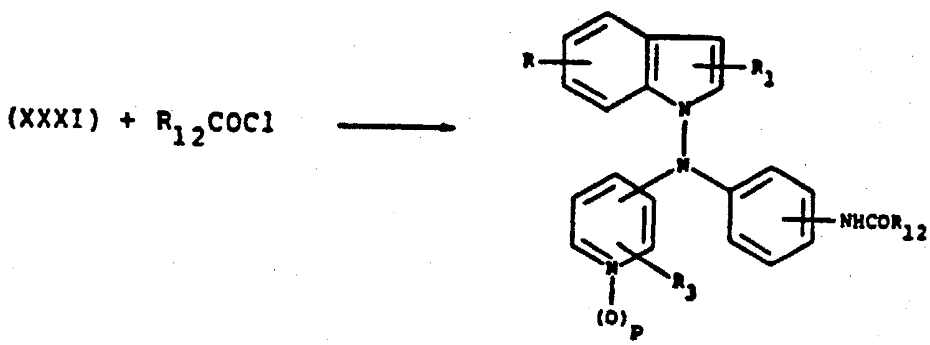
Substantially the same reaction technique as described in STEP P can be used to convert compound XXXI to a compound of formula XXXII below.



(XXXII)

STEP X

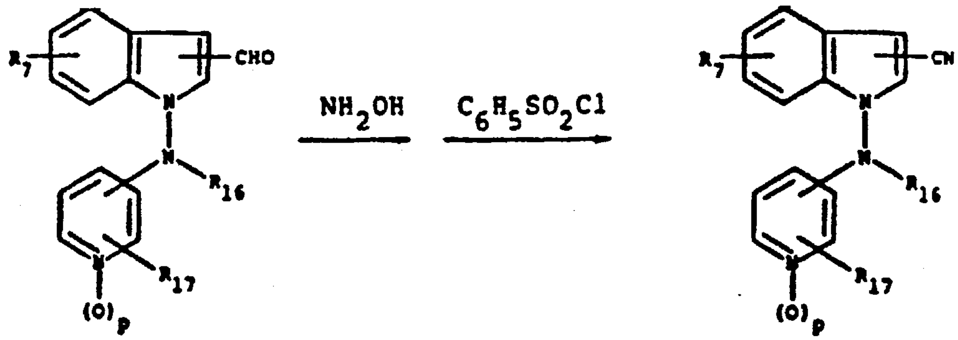
Substantially the same reaction technique as described in STEP Q can be used to convert compound XXXI to a compound of formula XXXIII below.



(XXXIII)

STEP Y

As an alternative to the foregoing steps, introduction of a cyano group into the 2-or 3-position of the indole ring can be accomplished by using, as a starting compound, the formyl compound of formula XXXIV and converting the formyl group into a cyano group. For this purpose, compound XXXIV is first reacted with hydroxylamine in a routine manner to obtain the corresponding oxime and thereafter the oxime is reacted with benzenesulfonyl chloride to obtain a nitrile compound of formula XXXV. The second step is typically conducted in a suitable solvent such as ethereal solvent by warming the reaction mixture at 60-100°C.



(XXXIV) (XXXV)

STEP Z

For the purpose of preparing a compound of formula I where R_2 is aminocarbonylloweralkyl, a compound of formula I where R_2 is loweralkoxycarbonylloweralkyl (preferably ethoxycarbonylloweralkyl) is reacted with ammonia in a manner known to the art.

The compounds of formula I of the invention are useful in the treatment of various memory dysfunctions characterized by decreased cholinergic function, such as Alzheimer's disease.

This utility is demonstrated by the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay, where they are generally active over a broader dose range than heretofore known compounds, a distinct therapeutic advantage.

Dark Avoidance Assay

In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed form the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

If scopolamine, an anticholinergic that is known to cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is countered by an active test compound, resulting in a greater interval before re-entry into the dark compartment.

The results for active compound are expressed as the percent of a group of animals in which the effect of scopolamine is countered, as manifested by an increased interval between being placed in the test chamber and re-entering the dark compartment.

The results of some of the compounds of this invention are presented in Table 1 along with the result of physostigmine.

TABLE 1

Compound	Dose mg/kg Body Weight s.c.	% of Animals With Scopolamine Induced Memory Deficit Reversed
Physostigmine (namely, (3aS-cis)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-pyrrolo[2,3-b]indol-5-ol, methyl carbamate)	0.31	20%
N-Methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	0.04	53%
N-(4-Pyridinyl)-1H-indol-1-amine maleate	0.31	33%
N-Propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	0.08	27%
N-Ethyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	0.63	33%

Additionally, some of the compounds of this invention exhibit antidepressant activities, which activities being particularly helpful for patients suffering from Alzheimer's disease. The antidepressant activities were evaluated in this invention on the basis of prevention of Tetrabenazine-induced ptosis in mice. The test method and results are described below.

Prevention Of Tetrabenazine-Induced Ptosis In Mice

Tetrabenazine (TBZ) induces behavioral depression with concomitant ptosis in mice similar to reserpine. Antidepressant compounds, both monoamineoxidase inhibitors and tricyclics, are known to prevent or antagonize these effects and the degree of antagonism correlates with clinical efficacy. The prevention of TBZ-induced ptosis in mice is used as a preliminary screen for possible antidepressant activity. The method used in this invention is as follows:

Male mice weighing 20 to 30 grams are used in test groups of five subjects. All compounds are dissolved or suspended with a suitable surfactant in distilled water and administered in volumes of 10 ml/kg of body weight. TBZ solution is made from the methanesulfonate salt and the concentration is adjusted to enable administration of 60 mg/kg of base by intraperitoneal (i.p.) injection.

The pretreatment time is measured from the time of dosing to observation. Therefore, when a 30-minute pretreat is utilized, drug and TBZ are given simultaneously. A control group received solvent and TBZ at intervals indentical to drug group. For a primary screen, the drug is administered i.p. and a group size of five is utilized. Eight animals/group are used for a dose range.

Thirty minutes after TBZ, the subjects are placed in individual plastic containers (10.5 x 8 x 6 inches) in

the presence of white noise and one minute after the transfer, they are scored for ptosis on the following scale: Eyes closed = 4, eyes 3/4 closed = 3, eyes 1/2 closed = 2, eyes 1/4 closed = 1, eyes open = Ø. The total score for each group of five in a primary screen will, therefore, be from Ø to 2Ø and these scores are used as indications of drug activity.

The vehicle control group score is used as a determinant of the validity of each test. If the control score is less than 17, the results are discarded and the test repeated. The calculation of percent inhibition of ptosis is:

$$\frac{\text{(Control Score - Drug Score)}}{\text{Control Score}} \times 100\%$$

For $ED_{5Ø}$ estimation, four or five doses are administered in order to bracket the estimated value and only vehicle control scores of 27 to 32 are accepted to assure the accuracy of the $ED_{5Ø}$ estimation.

Linear regression analysis is used to estimate $ED_{5Ø}$ values and 95% confidence intervals.

The results of some of the compounds of this invention are shown in Table 2 along with a result for desipramine (prior art compound).

TABLE 2

Compound	$ED_{5Ø}$ (mg/kg, p.o.)
N-methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	3.3
N-(4-pyridinyl)-1H-indol-1-amine maleate	3.3
N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	5.1
N-ethyl-N-(4-pyridinyl-1H-indol-1-amine maleate	5.6
N-methyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde maleate	9.7
N-ethyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde maleate	11.9
5-methoxy-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	29.8
(Prior Art Compound) Desipramine	2.3

Compounds I of the present invention are also useful as analgesic agents due to their ability to alleviate pain in mammals. The activity of the compounds is demonstrated in the 2-phenyl-1,4-benzoquinone-induced writhing (PQW) test in mice, a standard assay for analgesia [Proc. Soc. Exptl. Biol. Med., 95, 729 (1957)] and in modified Haffner's analgesia.

The latter assay is used to evaluate analgesic activity by measuring drug-induced changes in the sensitivity of mice to pressure stress by placing an artery clip (2 1/2 inches long) on their tail. The

procedure used is a modification of the test developed by Haffner, Dtsch. Med. Wschr. 55, 731 (1929), and it is described below.

METHOD:

Male mice (Charles River CD-1) from 18-3Ø grams are used for the test. An artery clip is applied to the root of the tail of a mouse (approximately 1/2 inch from the body) to induce pain. The animals quickly responds to this noxious stimuli by biting the clip or the location of the clip. This reaction time, the interval between stimulus onset and response, is recorded in 1/1Ø second increments by a stop watch.

For at time response, the screening dose (25 mg/kg) is administered subcutaneously 1Ø ml/kg) to the animal receiving food and water ad libitum before testing. Animals receiving the compound orally are fasted 18-24 hours before drug administration. Drug to be tested is prepared with distilled water and if insoluble, one drop of a surfactant is added.

Twenty-eight animals (seven/group) are administered the drug 15, 3Ø, 45 and 6Ø minutes prior to testing.

The cut-off time (CO) is determined by taking the ($\bar{x}$) average + 3 standard (SD) deviation of the combined response latencies of the control mice in all time periods.

$$CO = \bar{x} + 3\ SD\ (seconds)$$

Any reaction time, in subsequent drug tests, which is greater than the CO (for the same time period) therefore exceeds 99% of a norami Gaussian distribution and is called "positive response" indicative of analgesic activity. A time response indicates the period of greatest analgesic effect after dosing. The $ED_{5Ø}$ is determined at the peak time of drug activity. A minimum of three dose groups are used. $ED_{5Ø}$'s are calculated using computer analysis.

The results of some of the compounds of this invention are shown in Table 3 along with those of a prior art compound.

TABLE 3

ANALGESIC ACTIVITY ($ED_{5Ø}$, mg/kg, s.c.)

Compound	PQW	Modified Haffner's Analgesia
N-methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	3.2	16.3
N-(4-pyridinyl)-1H-indol-1-amine maleate	Ø.86	5.7
N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	5.1	31.Ø
3-ethyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine hydrochloride	Ø.9	1.Ø
3-ethenyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate	1.Ø	1.Ø
(Prior Art Compound) Pentazocin	1.3	3.9

Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, salicylic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 milligrams of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound. The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparations can be enclosed in disposable syringes or multiple dose vials made of glass or plastic.

Examples of the compounds of this invention include:

N-(4-pyridinyl)-1H-indol-1-amine;
N-methyl-N-(4-pyridinyl)-1H-indol-1-amine;
N-ethyl-N-(4-pyridinyl)-1H-indol-1-amine;
N-propyl-N-(4-pyridinyl)-1H-indol-1-amine;
5-methoxy-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine;
N-methyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde;
N-ethyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde;
N-(4-nitro-3-pyridinyl)-1H-indol-1-amine-N^1-oxide;
N-(4-amino-3-pyridinyl)-1H-indol-1-amine-N^1-oxide;
3-ethenyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine;
3-ethyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine;
5-chloro-N-(4-pyridinyl)-1H-indol-1-amine;
5-chloro-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine;
5-bromo-N-(4-pyridinyl)-1H-indol-1-amine;
5-bromo-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine; and

5-bromo-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine.

EXAMPLE 1

N-(4-Pyridinyl)-1H-indol-1-amine maleate

A solution of 1H-indol-1-amine (30 g), 4-chlorpyridine hydrochloride (34 g) and pyridine (18 g) in 250 ml of isopropanol was stirred at 85° for 1.5 hours, and thereafter cooled, stirred with ice-water, basified with sodium carbonate and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to a dark oil. This oil was purified by flash chromatography (silica, ethyl acetate) and thereafter by column chromatography (alumina, ether) to give 24 g of oil. A 3.6 g sample was purified by high performance liquid chromatography (HPLC hereafter) (silica, ethyl acetate) to give 3.5 g of oil. This oil was converted to the maleate salt and recrystallized twice from methanol/ether to give 3.8 g of needles, d 145-146°.

ANALYSIS:
Calculated for $C_{13}H_{11}N_3 \cdot C_4H_4O_4$:
62.76%C 4.65%H 12.92%N
Found:
62.62%C 4.81%H 12.73%N

EXAMPLE 2

N-Methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of N-(4-pyridinyl)-H-indol-1-amine (7.4 g) in 30 ml of dimethylformamide was added to an ice-cooled suspension of NaH (1.6 g of 60% NaH dispersion in mineral oil was washed with hexanes, the liquid portion was decanted and the residual solid was dispersed in 10 ml of dimethylformamide). After anion formation, a solution of dimethylsulfate (5 g) in 10 ml of dimethylformamide was added. After one hour of stirring at ambient temperature, the reaction mixture was stirred with ice-water and extracted with ether. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 8 g of oil. This oil was purified by flash chromatography (silica, ethyl acetete), column chromatography (alumina, ether) and HPLC (silica, ethyl acetate) to give 2.9 g of oil. This oil was converted to the maleate salt and was recrystallized twice from methanol/ether to give 2.1 g of crystals, mp 103-104°.

ANALYSIS:
Calculated for $C_{14}H_{13}N_3 \cdot C_4H_4O_4$:
63.70% 5.05%H 12.39%N
Found:
63.36%C 4.93%H 12.39%N

EXAMPLE 3

N-Ethyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

To an ice-cooled suspension of sodium hydride (1.7 g of 60% NaH dispersion in mineral oil was washed with hexanes, the liquid was decanted and the residual solid was dispersed in 5 ml of dimethylformamide) was slowly added a solution of N-(4-pyridinyl)-1H-indol-1-amine (7.6 g) in 25 ml of dimethylformamide. After anion formation, a solution of diethyl sulfate (6.4 g) in 10 ml of dimethylformamide was slowly added. After one hour, the mixture was stirred with ice-water and extracted with ethyl acetate. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 11 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 6.2 of oil. This oil was purified by column chromatography (alumina, ether) to give 6 g of oil. A 3 g sample was converted to the maleate salt and recrystallized from ethanol/ether and thereafter from methanol/ether to give 2.7 g of crystals, mp 119-120°.

ANALYSIS:
Calculated for $C_{15}H_{15}N_3 \bullet C_4H_4O_4$:
64.58%C 5.42%H 11.89%N
Found:
64.27%C 5.49%H 12.11%N

EXAMPLE 4

N-Propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of N-(4-pyridinyl)-1H-indol-1-amine (6 g) in 25 ml of dimethylformamide was slowly added to an ice-cooled suspension of NaH (1.3 g of 60% NaH dispersion in mineral oil was washed with hexanes, the liquid was decanted and the residual solid was dispersed in 5 ml of dimethylformamide). After anion formation, a solution of 1-bromopropane (4 g) in 5 ml of dimethylformamide was added. After one hour of stirring at ambient temperature, the reaction mixture was stirred with ice-water and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 8 g of oil. This oil was purified by HPLC (silica, ethyl acetate) and thereafter by column chromatography (alumina, ether) to give 6.4 g oil. This oil was converted to the maleate salt and recrystallized from methanol/ether to give 6.8 g of crystals, mp 115-116°.

ANALYSIS:
Calculated for $C_{16}H_{17}N_3 \bullet C_4H_4O_4$:
65.38%C 5.76%H 11.44%N
Found:
65.26%C 5.71%H 11.34%N

EXAMPLE 5

5-Methoxy-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

To an ice-cooled suspension of sodium hydride (0.5 g of 60% NaH dispersion in mineral oil was wahsed with hexanes, the liquid was decanted and the residual solid was dispersed in 5 ml of dimethylformamide)was slowly added a solution of 5-methoxy-N-(4-pyridinyl)-1H-indol-1-amine (2.3 g) in 20 ml of dimethylformamide. After anion formation, a solution of 1-bromopropane (1.4 g) in 5 ml of dimethylformamide was added. After one hour of stirring, the reaction mixture was stirred with ice-water and extracted

with dichloromethane. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 2.3 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 2.1 g of oil. This oil was converted to the maleate salt in ethanol/ether to give 2.0 g of crystals, mp 138-139°C.

ANALYSIS:
Calculated for $C_{17}H_{19}N_3O \cdot C_4H_4O_4$:
63.46%C 5.83%H 10.58%N
Found:
63.26%C 5.77%H 10.47%N

EXAMPLE 6

N-Methyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde maleate

To ice-cooled dimethylformamide (4 g) was slowly added phosphorous oxychloride (7 g). After complex formation, a solution of N-methyl-N-(4-pyridinyl)-1H-indol-1-amine (5 g) in 50 ml of dichloroethane was added. After one hour of stirring at 85°C, the reaction mixture was cooled, hydrolyzed with a solution of sodium acetate (5 g) in 25 ml of water, again cooled, basified with sodium carbonate and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, fitlered and concentrated to 6 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 4.6 of oil. This oil was converted to the maleate salt and recrystallized from ethanol/ether and thereafter from methanol/ether to give 2.6 g of crystals, d 162-163°.

ANALYSIS:
Calculated for $C_{15}H_{13}N_3O \cdot C_4H_4O_4$:
62.12%C 4.66%H 11.44%N
Found:
61.71%C 4.62%H 11.14%N

EXAMPLE 7

N-Ethyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde maleate

To ice-cooled dimethylformamide (2.2. g) was slowly added phosphorous oxychloride (4.5 g). After complex formation, a solution of N-ethyl-N-(4-pyridinyl)-1H-indol-1-amine (3.5 g) in 50 ml of dichloroethane was added. The mixture was stirred at 80° for one hour and thereafter hydrolyzed with a solution of sodium acetate (5 g) in 25 ml of water, cooled, basified with sodium carbonate and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 5 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 3.5 g of oil. This oil was converted to the maleate salt and recrystallized from ethanol/ether and thereafter from methanol/ether to give 3 g of solid, d 170-171°.

ANALYSIS:
Calculated for $C_{16}H_{15}N_3O \cdot C_4H_4O_4$:
62.98%C 5.02%H 11.02%N
Found:
62.97%C 5.08%H 11.06%N

EXAMPLE 8

N-(4-Nitro-3-pyridinyl)-1H-indol-1-amine N[1]-oxide

A solution of 3-fluoro-4-nitro-pyridine-N-oxide (5 g) and 1H-indol-1-amine (4.2 g) in 25 ml of ethanol was stirred four hours at reflux. The solution was cooled and the product collected and dried to give 4 g of solid, d 195°. This material was recrystallized from ethanol/ether to give 2.2 g of solid, d 200-201°.

ANALYSIS:
Calculated for $C_{13}H_{10}N_4O_3$:
57.77%C 3.73%H 20.74%N
Found:
57.56%C 3.74%H 20.53%N

EXAMPLE 9

N-(4-Amino-3-pyridinyl)-1H-indol-1-amine N[1]-oxide

A mixture of N-(4-nitro-3-pyridinyl)-1H-indol-1-amine N[1]-oxide (5 g) and 0.5 g of platinum oxide in 250 ml of ethanol was hydrogenated at 50 psi (pounds per square inch) for four hours. The mixture was filtered and the filtered liquid was concentrated to a dark residue which was purified by flash chromatography (silica, 10% methanol in dichloromethane) to give 2.5 g of solid, d 235°. This material was recrystallized from methanol/ether to give 2.1 g of crystals, d 235°.

ANALYSIS:
Calculated for $C_{13}H_{12}N_4O$:
64.98% 5.03%H 23.32%N
Found:
64.74%C 5.12%H 23.04%N

EXAMPLE 10

3-Ethenyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

To an ice-cooled suspension of methyltriphenylphosphonium bromide (13 g) in 100 ml of anhydrous ether was added potassium t-butoxide (4 g). After phosphorane formation, a solution of N-ethyl-N-(4-pyridinyl)-1H-indol-1-amine-3-carboxaldehyde (7.5 g) in 50 ml of ether and 50 ml of tetrahydrofuran was added. After one hour of stirring, the reaction mixture was stirred with water and extracted with ether. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 20 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 7 g of oil. A 3.5 g sample was converted to the maleate salt in ethanol and recrystallized from methanol/ether to give 3 g of crystals, mp 153-154°.

ANALYSIS:
Calculated for $C_{16}H_{15}N_3 \cdot C_4H_4O_4$:
65.74%C 5.24%H 11.50%N
Found:
65.94%C 5.39%H 11.45%N

EXAMPLE 11

3-Ethyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine hydrochloride

A solution of 3-ethenyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine (5 g) in 250 ml of ethanol containing 0.5 g of platinum oxide was hydrogenated at 50 psi for one hour. The mixture was filtered and the filtered liquid was concentrated to 5 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 3.5 g of oil. This oil was converted to the hydrochloride salt in ethanol/ether and recrystallized from methanol/ether to give 3.0 g of crystals, d 262°.

ANALYSIS:
Calculated for $C_{16}H_{17}N_3 \cdot HCl$:
66.77%C 6.30%H 14.60%N
Found:
66.87%C 6.33%H 14.57%N

EXAMPLE 12

5-Chloro-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of 5-chloro-1H-indol-1-amine (9 g), 4-chloropyridine hydrochloride (12 g) and pyridine (6.4 g) in 100 ml of isopropanol was stirred at reflux for one hour, cooled and stirred with ice-water, and the mixture was basified with sodium carbonate, extracted with dichloromethane and filtered. The organic extract was washed with water and saturated sodium chloride, was dried over anhydrous magnesium sulfate, filtered and concentrated to a dark oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 6.2 g of oil. This oil was converted to the maleate salt in methanol-ether to give 7 g of crystals, mp 148-150°C. A 2.6 g sample was recrystallized from methanol-ether to give 2.4 g of crystals, d 150-152°.

ANALYSIS:
Calculated for $C_{13}H_{10}ClN_3 \cdot C_4H_4O_4$:
56.75%C 3.92%H 11.68%N
Found:
56.71%C 4.00%H 11.62%N

EXAMPLE 13

5-Chloro-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of 5-chloro-N-(4-pyridinyl)-1H-indol-1-amine (3.3 g) in 15 ml of dimethylformamide was slowly added to an ice-cooled suspension of sodium hydride (0.65 g of 60% oil dispersion was washed with

hexanes) in 5 ml of dimethylformamide. After anion formation a solution of 1-bromopropane (2 g) in 5 ml of dimethylformamide was added. After one hour the reaction mixture was stirred with ice-water and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride, was dried over anhydrous magnesium sulfate, filtered and concentrated to 5 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 3.1 g of oil. This oil was converted to the maleate salt in ethanol-ether and thereafter recrystallized from methanol-ether to give 3.4 g of crystals, mp 130°.

ANALYSIS:
Calculated for $C_{16}H_{16}ClN_3 \cdot C_4H_4O_4$:
59.77%C 5.02%H 10.46%N
Found:
59.97%C 5.13%H 10.35%N

EXAMPLE 14

5-Bromo-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of 5-bromo-1H-indol-1-amine (13 g), 4-chloropyridine hydrochloride (14 g) and pyridine (7.2 g) in 100 ml of isopropanol was stirred at reflux for one hour, cooled and stirred with ice-water, and thereafter the mixture was basified with sodium carbonate, extracted with dichloromethane and filtered. The organic extract was washed with water and saturated sodium chloride, was dried over anhydrous magnesium sulfate, filtered and concentrated to a dark oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 11 g of oil. This oil was converted to the maleate salt in ethanol-ether to give 13 g of solid, d 155-157°. A three gram sample was recrystallized from methanol-ether to give 2.8 g of crystals, d 161-162°.

ANALYSIS:
Calculated for $C_{13}H_{10}BrN_3 \cdot C_4H_4O_4$:
50.51%C 3.49%H 10.40%N
Found:
50.46%C 3.56%H 10.40%N

EXAMPLE 15

5-Bromo-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of 5-bromo-N-(4-pyridinyl)-1H-indol-1-amine (2.7 g) in 20 ml of dimethylformamide was slowly added to an ice-cooled suspension of sodium hydride (0.45 g of 60% oil dispersion was washed with hexanes) in 5 ml of dimethylformamide. After anion formation a solution of dimethylsulfate (1.4 g) in 5 ml of dimethylformamide was added. After one hour the reaction mixture was stirred with ice-water and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride, was dried over anhydrous magnesium sulfate, filtered and concentrated to 2 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 1.4 g of oil. This oil was converted to the maleate salt in ethanol-ether to give 1.2 g of crystals, mp 110-111°.

ANALYSIS:
Calculated for $C_{14}H_{12}BrN_3 \cdot C_4H_4O_4$:
51.69%C 3.86%H 10.05%N
Found:
51.55%C 3.89%H 10.14%N

EXAMPLE 16

5-Bromo-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of 5-bromo-N-(4-pyridinyl)-1H-indol-1-amine (4.9 g) in 25 ml of dimethylformamide was slowly added to an ice-cooled suspension of sodium hydride (0.8 g of 60% oil dispersion was washed with hexanes) in 5 ml of dimethylformamide. After anion formation a solution of 1-bromopropane (2.5 g) in 5 ml of dimethylformamide was added. After one hour the reaction mixture was stirred with ice-water and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride, was dried over anhydrous magnesium sulfate, filtered and concentrated to 5 g of oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 4.5 g of oil. This oil was converted to the maleate salt in ethanol-ether to give 5.4 g of solid, d 150-152°. This solid was recrystallized from methanol-ether to give 4.8 g of crystals, d 157-158°.

ANALYSIS:
Calculated for $C_{16}H_{16}BrN_3 \bullet C_4H_4O_4$:
53.82%C 4.52%H 9.42%N
Found:
53.63%C 4.62%H 9.40%N

EXAMPLE 17

5-Nitro-N-(4-pyridinyl)-1H-indol-1-amine hydrochloride

A solution of 5-nitro-1H-indol-1-amine (4.5 g) and 4-chloropyridine hydrochloride (4.5 g) in 175 ml of isopropanol was stirred at reflux for two hours, another equivalent of 4-chlorpyridine hydrochloride was added and the mixture was refluxed for two additional hours. The reaction mixture was then cooled, stirred with water, basified with sodium carbonate and extracted with ethyl acetate. The organic extract was washed with water and saturated sodium chloride solution, was dried ($MgSO_4$), filtered and concentrated to 9 g of dark oil. This oil was purified by flash chromatography (silica, ethyl acetate) to give 3.8 g of light brown solid, m.p. 183-184°. This material was converted to the hydrochloride salt and recrystallized twice from methanol/ether to give 3.5 g of orange needles, d 300-302°.

ANALYSIS:
Calculated for $C_{13}H_{10}N_4O_2 \bullet HCl$:
55.71%C 3.81%H 19.28%N
Found:
53.55%C 3.77%H 19.17%N

EXAMPLE 18

5-Methyl-5-nitro-N-(4-Pyridinyl)-1H-indol-1-amine maleate

A solution of 5-nitro-N-(4-pyridinyl)-1H-indol-1-amine (6 g) in 20 ml of dimethylformamide was slowly added to an ice-cooled NaH suspension prepared by washing 1.2 g of 60 % NaH suspension in oil with hexanes and suspending the residue in 5 ml dimethylformamide. After the anion formation a solution of dimethyl sulfate (3.7 g) in 10 ml of dimethylformamide was added. After one hour the reaction mixture was stirred with water and extracted with ethyl acetate. The organic extract was washed with water and saturated sodium chloride solution, was dried ($MgSO_4$), filtered and concentrated to 6 g of dark oil. This was purified by flash chromatography (silica, ethyl acetate) to give 2.7 g of orange solid, m.p. 149-150°. This was converted to the maleate salt and recrystallized twice from methanol/ether to give 2.7 g of orange crystals, d 174-175°.

ANALYSIS:
Calculated for $C_{14}H_{12}N_4O_2{:}C_4H_4O_4$:
56.25%C 4.20%H 14.58%N
Found:
56.14%C 4.27%H 14.46%N

EXAMPLE 19

3-Methyl-N-(4-pyridinyl)-1H-indol-1-amine oxalate

To 200 ml of isopropanol were added 4-chloropyridine hydrochloride (7.5 g) and 3-methyl-1H-indole-1-amine (7.6 g). The mixture was stirred at 90°C for six hours, and thereafter poured into 400 ml of ice water, and stirred for five minutes. The pH was adjusted to 10 with Na_2Co_3 solution and then extracted with ethyl acetate. The organic layer was washed with water and dried (saturated NaCl, anhydrous $MgSO_4$).

After filtration, the solvent was evaporated to obtain 8.4 g of thick brown oil, which was eluted on a silica gel column with ethyl acetate via HPLC. The desired fractions were combined and concentrated to 7.4 g of brown oil. A 2.3 g sample of this oil was dissolved in 50 ml of ethanol, and the pH adjusted to 1 with an ethanolic solution of oxalic acid, and the solution was diluted with ether. The resultant white precipitate was collected and dried to give 4.0 g, d 130-135°C. This material was recrystallized from ethanol/ether (1:1) to give 3,8 g, d 137°C.

ANALYSIS:
Calculated for $C_{14}H_{13}N_3 \bullet C_2H_2O_4$:
61.33%C 4.83%H 13.41%N
Found:
61.41%C 4.96%H 13.28%N

EXAMPLE 20

3-Methyl-N-propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate

To a cold NaH suspension prepared by washing 0.8 g of 60 % NaH suspension in oil with hexanes and suspending the residue in 15 ml of dry DMF was added a solution of 3-methyl-N-(4-pyridinyl)-1H-indol-1-amine (4.0 g) in 25 ml of dry DMF in ten minutes.

The mixture was stirred at ambient temperature for thirty minutes, poured into 200 ml of ice water, stirred for five minutes, and then extracted with ethyl acetate. The organic layer was washed with water and dried (saturated NaCl, anhydrous $MgSO_4$).

After filtration, the solvent was evaporated to give 5 g of brown oil, which was eluted on a silica gel column with ethyl acetate via HPLC. The desired fractions were combined and concentrated to 2.6 g of brown oil.

This oil was dissolved in ether, the pH was adjusted to 1 with ethereal maleic acid, and the resultant white precipitate collected and dried to give, 4.0 g, d.: 148°C. This material was recrystallized from methanol/ether (1:10) to give 3.5 g of white crystals, m.p. 148-149°C.

ANALYSIS:
Calculated for $C_{17}H_{19}N_3 \bullet C_4H_4O_4$:
66.13%C 6.08%H 11.02%N
Found:
66.15%C 6.02%H 11.00%N

EXAMPLE 21

N-(3-Fluoro-4-pyridinyl)-3-methyl-1H-indol-1-amine

To a 200 ml of isopropanol were added 4-chloro-3-fluoropyridine hydrochloride (10 g) and 3-methyl-1H-indol amine (5.9 g). The mixture was stirred at 90°C for four hours, cooled and poured into 500 ml of ice water. The pH was adjusted to 10 with Na_2CO_3 solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried (saturated NaCl, anhydrous $MgSO_4$).

After filtration, the solvent was evaporated to give about 10 g of dark oil, which was eluted on a silica gel column first with dichloromethane, and then with ether/petroleum ether (1:1) via "flash chromatography". The desired fractions were combined and concentrated to a yellow solid, 6,2 g, m.p. 45°C. A sample of this material was recrystallized from isopropyl ether/hexanes (1:1) to give a yellow solid, m.p. 141-142°C.

ANALYSIS:
Calculated for $C_{14}H_{12}FN_3$:
69.69%C 5.02%H 17.42%N
Found:
69.52%C 5.01%H 17.57%N

EXAMPLE 22

N-(3-Fluoro-4-pyridinyl)-N-propyl-3-methyl-1H-indol-1-amine hydrochloride

To a NaH suspension prepared by washing 0.5 g of 60 % NaH suspension in oil with hexanes and suspending the residue in 10 ml DMF, was added a solution of N-(3-fluoro-4-pyridinyl)-3-methyl-1H-indol-1-amine (3.0 g) in 20 ml of DMF at ice-bath temperature in ten minutes. The mixture was stirred for an additional five minutes, and thereafter a solution of propyl bromide (1.2 ml) in 10 ml of DMF was added in five minutes.

The mixture was stirred at ambient temperature for thirty minutes, poured into 10 ml of ice-water, and then extracted with ethyl acetate. The organic layer was collected, washed with water and dried (saturated NaCl, anhydrous $MgSO_4$).

After filtration, the solvent was evaporated to give 4 g of brown oil, which was eluted on a silica column with 20 % ethyl acetate/DCM via HPLC. The desired fractions were combined and concentrated to a thick yellow oil, 3.4 g.

The oil was dissolved in ether, the pH adjusted to 1 with ethereal-HCl, and the resultant white precipitate collected and dried to give 3.4 g. This material was recrystallized from ethanol/ether (1:20) to give 2.7 g of white crystals, d 193°.

ANALYSIS:
Calculated for $C_{17}H_{18}FN_3$:HCl:
63.84%C 5.99%H 13.14%N
Found:
64.11%C 6.01%H 13.20%N

EXAMPLE 23

N-(2-Propen-1-yl)-N-(4-pyridinyl)-1H-indol-1-amine maleate

A solution of N-(4-pyridinyl)-1H-indol-1-amine (8 g) in 40 ml of dimethylformamide was added to an ice-cooled NaH suspension prepared by washing 2 g of 60 % NaH suspension in oil with hexanes and suspending the residue in 10 ml of dimethylformamide. After the anion formation a solution of allyl bromide (6 g) in 10 ml of dimethylformamide was added. After one hour the reaction mixture was stirred with ice-water and extracted with ethyl acetate. The organic extract was washed with water and saturated sodium chloride, dried ($MgSO_4$), filtered and concentrated to an oil. This oil was purified first by flash chromatography (silica, ethyl acetate) and then by column chromatography (alumina, ether) to give 5 g of oil. This oil was converted to the maleate salt in methanol/water to give 6 g of pale yellow solid, m.p. 105-107°. This is combined with 1.8 g product from a previous reaction and recrystallized from methanol/ether to give 5 g of pale yellow crystals, m.p. 111-112°.

ANALYSIS:
Calculated for $C_{16}H_{15}N_3 \bullet C_4H_4O_4$:
65.74%C 5.24%H 11.50%N
Found:
65.80%C 5.24%H 11.51%N

EXAMPLE 24

N-(3-Fluoro-4-pyridinyl)-N-propyl-1H-indol-1-amine hydrochloride

To an NaH suspension prepared by washing 0.6 g of 60 % NaH suspension in oil with hexanes and suspending the residue in 10 ml of cold DMF, was added a solution of N-(3-fluoro-4-pyridinyl)-1H-indol-1-amine in 25 ml of DMF.

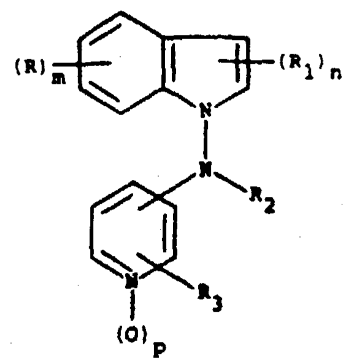
The mixture was stirred at 5°C for ten minutes, and thereafter a solution of bromopropane (1.4 ml) in 10 ml of DMF was added. The mixture was stirred at ambient temperature for thirty minutes, poured into 200 ml of ice water, stirred for five minutes, and extracted with ethyl acetate. The organic layer was washed with water and dried (saturated NaCl, anhydrous $MgSO_4$).

After filtration, the solvent was evaporated to give 3.2 g of brown oil, which was eluted on a silica gel column with 10 % ethyl acetate/ DCM via HPLC. The desired fractions were combined and concentrated to 2.4 g of brown oil, which was dissolved in 40 ml of absolute ethanol. The pH was adjusted to 1 with ethereal-HCl, and the solution was diluted with 400 ml of ether. The resultant off-white precipitate was collected and dried to give 2.1 g, m.p. 198-200°C dec.

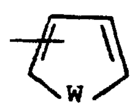
ANALYSIS:
Calculated for $C_{16}H_{16}FN_3 \bullet HCl$:
62.85%C 5.60%H 13.74%N
Found:
62.80%C 5.60%H 13.66%N

Claims

1. A compound having the formula



where m is 1 or 2; n is 1 or 2; P is Ø or 1; each R is independently hydrogen, halogen, loweralkyl, loweralkoxy, hydroxy, nitro, amino, loweralkylamino, loweralkylcarbonylamino, cyano, formyl, loweralkoxycarbonyl, loweralkylthio or loweralkoxycarbonylloweralkylthio; each R_1 is independently hydrogen, loweralkyl, loweralkenyl, formyl, loweralkylcarbonyl, arylloweralkylcarbonyl, arylcarbonyl, halogen, arylloweralkenyl, arylloweralkyl, heteroarylloweralkenyl, heteroaryloweralkyl, cyanoloweralkenyl, cyanoloweralkyl, methoxyloweralkenyl, methoxyloweralkyl, loweralkoxycarbonylloweralkenyl, loweralkoxycarbonylloweralkyl, cycloalkylloweralkenyl or cycloalkylloweralkyl, the term heteroaryl signifying a group of the formula



where W is O, S, NH or CH=N, cyano, $-CH(OH)R_4$, $-C(OH)R_4R_5$ or $-CH_2OR_5$, R_4 being hydrogen, loweralkyl, arylloweralkyl or aryl and R_5 being loweralkyl, arylloweralkyl or aryl; each R_2 is independently hydrogen, loweralkyl, loweralkenyl, loweralkynyl, loweralkoxycarbonylloweralkyl, loweralkylaminocarbonylloweralkyl, aminocarbonylloweralkyl, arylloweralkyl, phenyl, nitrophenyl, cyanophenyl, trifluoromethylphenyl, aminophenyl, loweralkanoylaminophenyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, loweralkylaminocarbonyl, arylloweralkylaminocarbonyl, arylaminocarbonyl, alkanoyl, arylloweralkanoyl, aroyl, alkenoyl, alkynoyl or $-R_6-NR'R''$ where R_6 is loweralkylene, loweralkenylene or loweralkynylene and R' and R'' are each independently loweralkyl or alternatively the group $-NR'R''$ as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl; and R_3 is hydrogen, nitro, amino, halogen, loweralkanoylamino, arylloweralkanoylamino, aroylamino, alkylamino, arylloweralkylamino or loweralkyl; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound as defined in claim 1, where m is 1, n is 1 and p is zero.

3. A compound as defined in claim 2, where R is hydrogen, loweralkyl or loweralkoxy, R_1 is hydrogen, loweralkyl, loweralkenyl or formyl, R_2 is hydrogen, loweralkyl or arylloweralkyl and R_3 is hydrogen, halogen, nitro or amino.

4. The compound as defined in claim 1, which is N-methyl-N-(4-pyridinyl)-1H-indol-1-amine or a pharmaceutically acceptable acid addition salt thereof.

5. The compound as defined in claim 1, which is N-(4-pyridinyl)-1H-indol-1-amine or a pharmaceutically acceptable acid addition salt thereof.

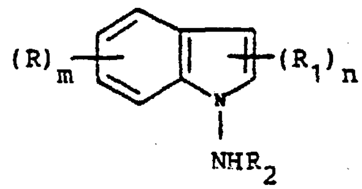
6. The compound as defined in claim 1, which is N-propyl-N-(4-pyridinyl)-1H-indol-1-amine, or a pharmaceutically acceptable acid addition salt thereof.

7. The compound as defined in claim 1, which is 3-ethyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine, or a pharmaceutically acceptable acid addition salt thereof.

8. The compound as defined in claim 1, which is 3-ethenyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine, or a pharmaceutically acceptable acid addition salt thereof.

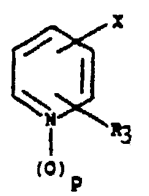
9. A process for the preparation of a compound as defined in claim 1, which comprises

a) reacting a compound of the formula II



II

where m is 1 or 2 and n is 1 or 2, R is hydrogen, halogen, loweralkyl, loweralkoxy, nitro, cyano, formyl, loweralkylthio or loweralkoxycarbonylloweralkylthio, R_1 is hydrogen, loweralkyl, halogen or cyano and R_2 is hydrogen or loweralkyl, with a compound of the formula III

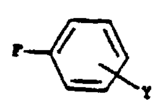


III

where X is chlorine or fluorine, R_3 is hydrogen, nitro, halogen or loweralkyl and p is 0 or 1, to afford a compound of the formula I, where R, R_1, R_2 and R_3 are as defined,

b) optionally treating a compound of the formula I as obtained in step a) where R_2 is hydrogen, with a strong base and reacting the obtained anion with a compound of the formula R_2Cl, where R_2 is loweralkyl, loweralkoxycarbonylloweralkyl, loweralkenyl, loweralkynyl, arylloweralkyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl or aryloxycarbonyl, to afford a compound of the formula I, where m, n, p R, R_1, R_3 are as defined in step a) and R_2 is as defined above,

c) optionally treating a compound of the formula I as obtained in step a) where R_2 is hydrogen, with a strong base and reacting the obtained anion with a compound of the formula



where Y is nitro, cyano or trifluoromethyl, to afford a compound of the formula I, where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is nitrophenyl, cyanophenyl or trifluoromethylphenyl,

d) optionally reacting a compound of the formula I as obtained in step a), where R_2 is hydrogen, with a loweralkyl isocyanate, arylloweralkyl isocyanate or aryl isocyanate of the formula $R_{12}NCO$ where R_{12} is loweralkyl, arylloweralkyl or aryl to afford a compound of the formula I, where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is loweralkylaminocarbonyl, arylloweralkylaminocarbonyl or arylaminocarbonyl,

e) optionally reacting a compound of the formula I as obtained in step a) where R_2 is hydrogen, with a compound of the formula $R_{13}COCl$ where R_{13} is alkyl, arylloweralkyl, aryl, alkenyl or alkynyl to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is alkanoyl, arylloweralkanoyl, aroyl, alkenoyl or alkynoyl,

f) optionally reacting a compound of the formula I as obtained in step a) where R_2 is hydrogen with a strong base and then reacting the product with a diloweralkylsulfate to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is loweralkyl,

g) optionally objecting a compound of the formula I as obtained in step b) where R_2 is $-CH_2C\equiv CH$ to a Mannich reaction with formaldehyd and a secondary amine of the formula $HNR'R''$, where R' and R'' are independently loweralkyl or R' and R'' taken together are 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step b) and R_2 is the group $-CH_2C\equiv CCH_2NR'R''$ where R' and R'' are as defined above,

h) optionally hydrogenating a compound of the formula I as obtained in step g) to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is the group $-CH_2CH=CHCH_2NR'R''$ or $-(CH_2)_4NR'R''$ where R' and R'' are as defined in step g),

i) optionally reacting a compound of the formula I where m, n, p, R and R_3 are as defined in step a), R_1 is hydrogen and R_2 is loweralkyl, loweralkoxycarbonylloweralkyl, arylloweralkyl, aryl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, alkanoyl, arylloweralkanoyl or aroyl, with a suitable chlorinating agent to afford the 3-chloro-derivative of a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined above,

j) optionally reacting a compound of the formula I where m, n, p and R are as defined in step a), R_1 is hydrogen, R_2 is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl, and R_3 is hydrogen, nitro, halogen or loweralkyl, either with phosphorous oxychloride and dimethylformamide to afford a compound of the formula I where R_1 is the formyl group at 3-position, or with sec. butyllithium and reacting the resulting lithio compound with N-formyl-N-methyl-aniline to afford a compound of the formula I where R_1 is the formyl group at 2-position,

k) optionally reacting a compound of the formula I where m, n, p and R are as defined in step a), R_1 is hydrogen, R_2 is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl and R_3 is hydrogen, nitro, halogen, or loweralkyl either with a loweralkanoyl-, arylloweralkanoyl-or aroyl chloride of formula $R_{12}COCl$ in the presence of zinc chloride to afford a compound of the formula I where R_1 is loweralkanoyl, arylloweralkanoyl or aroyl, or with sec-butyllithium and reacting the resultant lithio compound with $R_{12}COCl$ to afford a compound of the formula I where the substituent R_1 is in 2-position,

l) optionally reducing a compound of the formula I where m, n, p and R are as defined in step a), R_1 is loweralkanoyl, arylloweralkanoyl or aroyl, R_2 is loweralkyl, arylloweralkyl or aryl and R_3 is hydrogen, halogen or loweralkyl, either with $NaBH_4$, $LiAlH_4$ or borane complexes to afford a compound of the formula I where R_1 is the group $-CH(OH)R_4$ where R_4 is hydrogen, loweralkyl, arylloweralkyl or aryl, or with a Grignard reagent of the formula R_5MgBr to afford a compound of the formula I, where R_1 is the group

$$\begin{array}{c} OH \\ -C-R_4 \\ R_5 \end{array}$$

where R_5 is loweralkyl, arylloweralkyl or aryl,

m) optionally hydrogenating a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above, and R_3 is the nitro group, in the presence of a catalyst, to afford a compound of the formula I, where R_3 is the amino group,

n) optionally hydrolyzing a compound of the formula I, where m, n, p, R, R_1 are as defined in formula I above, R_3 is as defined in step a) and R_2 is the loweralkoxycarbonyl group, to afford a compound of the formula I where R_2 is hydrogen,

o) optionally reacting a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above, and R_3 is the amino group, with phenyl formate, to afford a compound of the formula I, where R_3 is the formylamino group,

p) optionally reacting a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above, and R_3 is the amino group, with an acyl chloride of the formula $R_{12}COCl$ or acid anhydride of the formula $R_{12}CO-O-COR_{13}$, where R_{12} is loweralkyl, arylloweralkyl or aryl, to afford a compound of the formula I where R_3 is loweralkanoylamino, arylloweralkanoylamino or aroylamino,

q) optionally reacting a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above and R_3 is hydrogen with loweralkyl lithium to afford a compound of the formula I where R_3 is loweralkyl,

r) optionally reacting a compound of the formula I, where m, n, p and R are as defined in formula I above, R_2 is loweralkyl, arylloweralkyl or aryl, R_3 is hydrogen, halogen or loweralkyl and R_1 is the group $-CH_2OH$, with a strong alkali metal base and reacting the resultant alkoxide ion with a loweralkyl halide, arylloweralkyl halide or aryl halide of the formula R_5X to afford a compound of the formula I, where R_1 is the group $-CH_2OR_5$,

s) optionally subjecting a compound of the formula I, where m, n, p and R are as defined in step a), R_1 is -CHO, R_2 is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl, and R_3 is hydrogen, NO_2, halogen or loweralkyl, to a Wittig reaction with an ylide of the formula (C_6H_5)-

$_3P=CR_{20}R_{21}$, where R_{20} and R_{21} are each independently hydrogen, loweralkyl, aryl, arylloweralkyl, heteroaryl, heteroarylloweralkyl, cyano, methoxy, loweralkoxycarbonyl or, taken together, form a cycloalkylidene, to afford a compound of the formula I where R_1 is the group $-CH=CR_{20}R_{21}$,

t) optionally catalytically hydrogenating a compound of the formula I as obtained in step s), to afford a compound of the formula I where R_1 is loweralkyl, arylloweralkyl, heteroarylloweralkyl, cyanoloweralkyl, methoxyloweralkyl, loweralkoxycarbonylloweralkyl or cycloalkylloweralkyl,

u) optionally catalytically hydrogenating a compound of the formula I where m, n, p, R, R_1 and R_2 are as defined in formula 1 above, and R_2 is nitrophenyl, to afford a compound of the formula I where R_2 is aminophenyl,

v) optionally reacting a compound of the formula I as obtained in step u) with phenyl formate to afford a compound of the formula I where R_2 is formylaminophenyl,

w) optionally reacting a compound of the formula I as obtained in step u) with an acyl chloride of the formula $R_{12}COCl$ or acid anhydride of the formula R_{12}-CO-O-COR_{12} where R_{12} is loweralkyl, to afford a compound of the formula I where R_2 is loweralkanoylaminophenyl,

x) optionally reacting a compound of the formula I as obtained in step j) where R_1 is -CHO with hydroxylamine to afford the corresponding oxime and reacting this oxime with benzenesulfonyl chloride to afford a compound of the formula I where R_1 is the radical -CN,

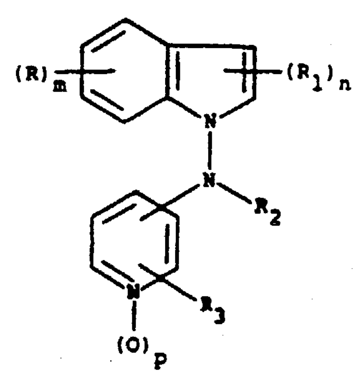
y) optionally reacting a compound of the formula I, where R_1 is loweralkoxycarbonylloweralkyl with ammonia to afford a compound of the formula I where R_2 is the group aminocarbonylloweralkyl.

10. A pharmaceutically composition which comprises a compound as defined in claim 1 as the active ingredient and a pharmaceutically acceptable carrier therefor.

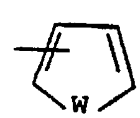
11. Use of a compound as defined in claim 1 for the preparation of a medicament having memory enhancing, pain alleviating and/or depression alleviating activities.

Claims for the following Contracting States: ES, GR

1. A process for the preparation of a compound of formula I



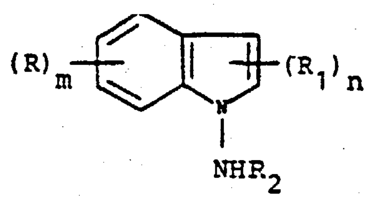
where m is 1 or 2; n is 1 or 2; P is 0 or 1; each R is independently hydrogen, halogen, loweralkyl, loweralkoxy, hydroxy, nitro, amino, loweralkylamino, loweralkylcarbonylamino, cyano, formyl, loweralkoxycarbonyl, loweralkylthio or loweralkoxycarbonylloweralkylthio; each R_1 is independently hydrogen, loweralkyl, loweralkenyl, formyl, loweralkylcarbonyl, arylloweralkylcarbonyl, arylcarbonyl, halogen, arylloweralkenyl, arylloweralkyl, heteroarylloweralkenyl, heteroaryloweralkyl, cyanoloweralkenyl, cyanoloweralkyl, methoxyloweralkenyl, methoxyloweralkyl, loweralkoxycarbonylloweralkenyl, loweralkoxycarbonylloweralkyl, cycloalkylloweralkenyl or cycloalkylloweralkyl, the term heteroaryl signifying a group of the formula



where W is O, S, NH or CH=N, cyano, $-CH(OH)R_4$, $-C(OH)R_4R_5$ or $-CH_2OR_5$, R_4 being hydrogen,

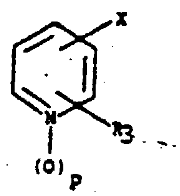
loweralkyl, arylloweralkyl or aryl and R_5 being loweralkyl, arylloweralkyl or aryl; each R_2 is independently hydrogen, loweralkyl, loweralkenyl, loweralkynyl, loweralkoxycarbonylloweralkyl, loweralkylaminocarbonylloweralkyl, aminocarbonylloweralkyl, arylloweralkyl, phenyl, nitrophenyl, cyanophenyl, trifluoromethylphenyl, aminophenyl, loweralkanoylaminophenyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, loweralkylaminocarbonyl, arylloweralkylaminocarbonyl, arylaminocarbonyl, alkanoyl, arylloweralkanoyl, aroyl, alkenoyl, alkynoyl, or $-R_6-NR'R''$ where R_6 is loweralkylene, loweralkenylene or loweralkynylene and R' and R'' are each independently loweralkyl or alternatively the group $-NR'R''$ as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl; and R_3 is hydrogen, nitro, amino, halogen, loweralkylamino, arylloweralkanoylamino, aroylamino, alkylamino, arylloweralkylamino or loweralkyl; or a pharmaceutically acceptable acid addition salt thereof, which comprises

a) reacting a compound of the formula II



II

where m is 1 or 2 and n is 1 or 2, R is hydrogen, halogen, loweralkyl, loweralkoxy, nitro, cyano, formyl, loweralkylthio or loweralkoxycarbonylloweralkylthio, R_1 is hydrogen, loweralkyl, halogen or cyano and R_2 is hydrogen or loweralkyl, with a compound of the formula III

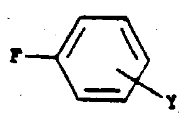


III

where X is chlorine or fluorine, R_3 is hydrogen, nitro, halogen or loweralkyl and p or 0 or 1, to afford a compound of the formula I, where R, R_1, R_2 and R_3 are as defined,

b) optionally treating a compound of the formula I as obtained in step a) where R_2 is hydrogen, with a strong base and reacting the obtained anion with a compound of the formula R_2Cl, where R_2 is loweralkyl, loweralkoxycarbonylloweralkyl, loweralkenyl, loweralkynyl, arylloweralkyl, loweralkoxycarbonyl, arylloweralkoxycarbonyl or aryloxycarbonyl, to afford a compound of the formula I, where m, n, p, R, R_1, R_3 are as defined in step a) and R_2 is as defined above,

c) optionally treating a compound of the formula I as obtained in step a) where R_2 is hydrogen, with a strong base and reacting the obtained anion with a compound of the formula



where Y is nitro, cyano or trifluoromethyl, to afford a compound of the formula I, where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is nitrophenyl, cyanophenyl or trifluoromethylphenyl,

d) optionally reacting a compound of the formula I as obtained in step a), where R_2 is hydrogen, with a loweralkyl isocyanate, arylloweralkyl isocyanate or aryl isocyanate of the formula $R_{12}NCO$ where R_{12} is loweralkyl, arylloweralkyl or aryl to afford a compound of the formula I, where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is loweralkylaminocarbonyl, arylloweralkylaminocarbonyl or arylaminocarbonyl,

e) optionally reacting a compound of the formula I as obtained in step a) where R_2 is hydrogen, with a compound of the formula $R_{13}COCl$ where R_{13} is alkyl, arylloweralkyl, aryl, alkenyl or alkynyl to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is alkanoyl, arylloweralkanoyl, aroyl, alkenoyl or alkynoyl,

f) optionally reacting a compound of the formula I as obtained in step a) where R_2 is hydrogen with a strong base and then reacting the product with a diloweralkylsulfate to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is loweralkyl,

g) optionally objecting a compound of the formula I as obtained in step b) where R_2 is $-CH_2C=CH$ to a Mannich reaction with formaldehyd and a secondary amine of the formula $HNR'R''$, where R' and R'' are independently loweralkyl or R' and R'' taken together are 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, 4-loweralkyl-1-piperazinyl or 4-aryl-1-piperazinyl to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step b) and R_2 is the group $-CH_2C=CCH_2NR'R''$ where R' and R'' are as defined above,

h) optionally hydrogenating a compound of the formula I as obtained in step g) to afford a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in step a) and R_2 is the group $-CH_2CH=CHCH_2NR'R''$ or $-(CH_2)_4NR'R''$ where R' and R'' are as defined in step g),

i) optionally reacting a compound of the formula I where m, n, p, R and R_3 are as defined in step a), R_1 is hydrogen and R_2 is loweralkyl, loweralkoxycarbonylloweralkyl, arylloweralkyl, aryl, loweralkoxycarbonyl, arylloweralkoxycarbonyl, aryloxycarbonyl, alkanoyl, arylloweralkanoyl or aroyl, with a suitable chlorinating agent to afford the 3-chloro-derivative of a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined above,

j) optionally reacting a compound of the formula I where m, n, p and R are as defined in step a), R_1 is hydrogen, R_2 is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl, and R_3 is hydrogen, nitro, halogen or loweralkyl, either with phosphorous oxychloride and dimethylformamide to afford a compound of the formula I where R_1 is the formyl group at 3-position, or with sec. butyllithium and reacting the resulting lithio compound with N-formyl-N-methyl-aniline to afford a compound of the formula I where R_1 is the formyl group at 2-position,

k) optionally reacting a compound of the formula I where m, n, p and R are as defined in step a), R_1 is hydrogen, R_2 is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl and R_3 is hydrogen, nitro, halogen or loweralkyl either with a loweralkanoyl-, arylloweralkanoyl-or aroyl chloride of formula $R_{12}COCl$ in the presence of zinc chloride to afford a compound of the formula I where R_1 is loweralkanoyl, arylloweralkanoyl or aroyl, or with sec-butyllithium and reacting the resultant lithio compound with $R_{12}COCl$ to afford a compound of the formula I where the substituent R_1 is in 2-position,

l) optionally reducing a compound of the formula I where m, n, p and R are as defined in step a), R_1 is loweralkanoyl, arylloweralkanoyl or aroyl, R_2 is loweralkyl, arylloweralkyl or aryl and R_3 is hydrogen, halogen or loweralkyl, either with $NaBH_4$, $LiAlH_4$ or borane complexes to afford a compound of the formula I where R_1 is the group $-CH(OH)R_4$ where R_4 is hydrogen, loweralkyl, arylloweralkyl or aryl, or with a Grignard reagent of the formula R_5MgBr to afford a compound of the formula I, where R_1 is the group

$$\begin{array}{c} OH \\ -C-R_4 \\ R_5 \end{array}$$

where R_5 is loweralkyl, arylloweralkyl or aryl,

m) optionally hydrogenating a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above, and R_3 is the nitro group, in the presence of a catalyst, to afford a compound of the formula I, where R_3 is the amino group,

n) optionally hydrolyzing a compound of the formula I, where m, n, p, R, R_1 are as defined in formula I above, R_3 is as defined in step a) and R_2 is the loweralkoxycarbonyl group, to afford a compound of the formula I where R_2 is hydrogen,

o) optionally reacting a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above, and R_3 is the amino group, with phenyl formate, to afford a compound of the formula I, where R_3 is the formylamino group,

p) optionally reacting a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above, and R_3 is the amino group, with an acyl chloride of the formula $R_{12}COCl$ or acid anhydride of the formula $R_{12}CO\text{-}O\text{-}COR_{13}$, where R_{12} is loweralkyl, arylloweralkyl or aryl, to afford a compound of the formula I where R_3 is loweralkanoylamino, arylloweralkanoylamino or aroylamino,

q) optionally reacting a compound of the formula I, where m, n, p, R, R_1 and R_2 are as defined in formula I above and R_3 is hydrogen with loweralkyl lithium to afford a compound of the formula I where R_3 is loweralkyl,

r) optionally reacting a compound of the formula I, where m, n, p and R are as defined in formula I above, R_2 is loweralkyl, arylloweralkyl or aryl, R_3 is hydrogen, halogen or loweralkyl and R_1 is the group $-CH_2OH$, with a strong alkali metal base and reacting the resultant alkoxide ion with a loweralkyl halide, arylloweralkyl halide or aryl halide of the formula R_5X to afford a compound of the formula I, where R_1 is the group $-CH_2OR_5$,

s) optionally subjecting a compound of the formula I, where m, n, p and R are as defined in step a), R_1 is -CHO, R_2 is loweralkyl, loweralkoxycarbonyl, alkanoyl, alkenoyl, alkynoyl, arylloweralkanoyl or aroyl, and R_3 is hydrogen, NO_2, halogen or loweralkyl, to a Wittig reaction with an ylide of the formula $(C_6H_5)_3P=CR_{20}R_{21}$, where R_{20} and R_{21} are each independently hydrogen, loweralkyl, aryl, arylloweralkyl, heteroaryl, heteroarylloweralkyl, cyano, methoxy, loweralkoxycarbonyl or, taken together, form a cycloalkylidene, to afford a compound of the formula I where R_1 is the group $-CH=CR_{20}R_{21}$,

t) optionally catalytically hydrogenating a compound of the formula I as obtained in step s), to afford a compound of the formula I where R_1 is loweralkyl, arylloweralkyl, heteroarylloweralkyl, cyanoloweralkyl, methoxyloweralkyl, loweralkoxycarbonylloweralkyl or cycloalkylloweralkyl,

u) optionally catalytically hydrogenating a compound of the formula I where m, n, p, R, R_1 and R_3 are as defined in formula I above, and R_2 is nitrophenyl, to afford a compound of the formula I where R_2 is aminophenyl,

v) optionally reacting a compound of the formula I as obtained in step u) with phenyl formate to afford a compound of the formula I where R_2 is formylaminophenyl,

w) optionally reacting a compound of the formula I as obtained in step u) with an acyl chloride of the formula $R_{12}COCl$ or acid anhydride of the formula R_{12}-CO-O-COR_{12} where R_{12} is loweralkyl, to afford a compound of the formula I where R_2 is loweralkanoylaminophenyl,

x) optionally reacting a compound of the formula I as obtained in step j) where R_1 is -CHO with hydroxylamine to afford the corresponding oxime and reacting this oxime with benzenesulfonyl chloride to afford a compound of the formula I where R_1 is the radical -CN,

y) optionally reacting a compound of the formula I, where R_1 is loweralkoxycarbonylloweralkyl with ammonia to afford a compound of the formula I where R_2 is the group aminocarbonylloweralkyl.

2. A process as defined in claim 1 where m is 1, n is 1 and p is zero.

3. A process as defined in claim 2, where R is hydrogen, loweralkyl or loweralkoxy, R_1 is hydrogen, loweralkyl, loweralkenyl or formyl, R_2 is hydrogen, loweralkyl or arylloweralkyl and R_3 is hydrogen, halogen, nitro or amino.

4. A process as defined in claim 1, where the compound N-methyl-N-(4-pyridinyl)-1H-indol-1-amine or a pharmaceutically acceptable acid addition salt thereof is prepared.

5. A process as defined in claim 1, where the compound N-(4-pyridinyl)-1H-indol-1-amine or a pharmaceutically acceptable acid addition salt thereof is prepared.

6. A process as defined in claim 1, where the compound N-propyl-N-(4-pyridinyl)-1H-indol-1-amine, or a pharmaceutically acceptable acid addition salt thereof is prepared.

7. A process as defined in claim 1, where the compound 3-ethyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine, or a pharmaceutically acceptable acid addition salt thereof is prepared.

8. A process as defined in claim 1, where the compound 3-ethenyl-N-methyl-N-(4-pyridinyl)-1H-indol-1-amine or a pharmaceutically acceptable addition salt thereof is prepared.

9. Use of a compound as defined in claim 1 for the preparation of a medicament having memory enhancing, pain alleviating and/or pain alleviating activities.